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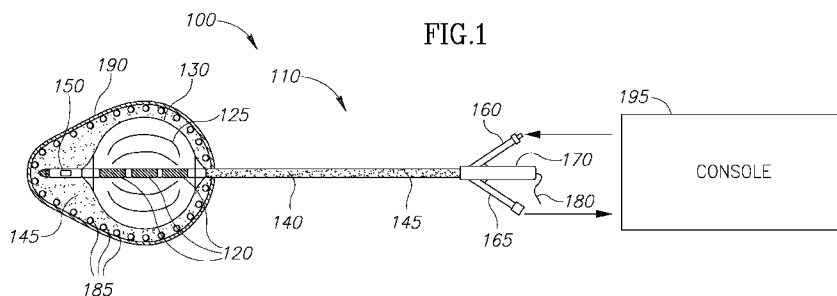
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(54) Title: ULTRASONIC URINARY BLADDER DRUG DELIVERY



(57) Abstract: A kit comprising: a urinary catheter comprising a first and a second longitudinal lumens; an ultrasonic transducer disposed about said catheter; a balloon mounted on said catheter, and enclosing said transducer; and a reservoir containing an acoustic coupling medium, wherein: said catheter further comprises a first opening in said first longitudinal lumen, said first opening disposed inside said balloon and configured to inflate said balloon with at least some of said acoustic coupling medium, said catheter further comprises a second opening in said second longitudinal lumen, said second opening disposed outside said balloon and configured to deliver a therapeutic fluid into the urinary bladder, around said balloon, and activation of said transducer in said urinary bladder causes cavitation bubbles to form in said therapeutic fluid adjacent an internal surface of the urinary bladder, and little or no cavitation bubbles are formed in said acoustic coupling medium in said balloon.

ULTRASONIC URINARY BLADDER DRUG DELIVERY

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Patent Application No. 62/138,573 filed March 26, 2015, U.S. Provisional Patent Application No. 62/203,109 filed November 17, 2015, and U.S. Provisional Patent Application No. 62/273,503 filed December 31, 2015 the contents of which are incorporated herein by reference in their entirety.

FIELD OF INVENTION

[0002] The present invention relates to the field of intravesical therapy.

BACKGROUND

[0003] Intravesical treatment is a method that allows direct transfer of drugs into the urinary bladder (or simply 'bladder'). Standard intravesical treatment involves insertion of a urinary catheter through the urethra and into the bladder. Lumens that run along the catheter length constitute direct route in and out of the bladder, thereby allowing drainage of the bladder and irrigation with drug solutions. This site-specific treatment may have the advantage of delivering drugs directly into the bladder, as opposed to non-specific systemic treatment given orally or infused directly into the blood system. In bladder cancer treatment, for example, intravesical drug delivery may allow the delivery of cytotoxic chemotherapy drugs directly to the treatment site, thus sparing healthy tissues that would otherwise be affected under systemic treatment. Intravesical drug delivery is also used in treatments of many other ailments of the bladder, such as of cystitis, overactive bladder, and bladder infections.

[0004] Intravesical therapy may involve several challenges and limitations. The bladder inner surface is covered with transitional epithelium lining called urothelium, and glycosaminoglycans (GAG) units found on the urothelium. Both the urothelium and the GAG units may function as an important barrier to toxins and waste found in the urine, giving the bladder wall its low permeability characteristic. However, this compact and tight

barrier may also restrict effective penetration of therapeutic drugs delivered into the bladder during intravesical treatments. Some therapeutic molecules may not penetrate the bladder barrier at all. For example, Botox, which is a large toxin that may be delivered to the bladder wall for the treatment of overactive bladder, may not penetrate the bladder barrier. Hence, under standard practice Botox is injected into the bladder using a cystoscope and a needle. In this procedure a cystoscope and a needle are inserted into the bladder through the urethra and the Botox is injected to the bladder detrusor at 20-30 different sites. This procedure is invasive, requires anesthesia, and involves some risks associated with needle injections. Also Botox delivery profile is not uniform- Injections of the Botox to discrete injections sites result in areas in the bladder with excess of Botox, and region in the bladder with no Botox at all.

[0005] Ultrasound cavitation is a major mechanism by which ultrasound increases tissue permeability. According to theory, cavitation bubbles collapse on the tissue with high energy and open up pores in the tissue, which results in the increased permeability of the tissue to therapeutic drugs. There may be two challenges when cavitation is concerned. The first is that cavitation may need to form in a solution in a close proximity to the tissue surface in order to increase drug delivery. The second is that cavitation bubbles may usually form near or on the ultrasonic transducer surface, thereby blocking the ultrasonic waves (see, for example: Terahara T. et al., Dependence of low-frequency sonophoresis on Ultrasound parameters; distance of the horn and intensity. *International Journal of Pharmaceutics*. 2002 Mar 20; 235(1-2): 35-42).

[0006] Overactive bladder is a prevalent condition that has a significant impact on quality of life. The usual treatment approach is both behavioral and pharmacological. The first-line pharmacological treatment commonly utilizes anticholinergic agents, which may be limited by their tolerability, efficacy, and long-term compliance. Additional therapeutic agents include mirabegron and botulinum toxin, which may reduce the anticholinergic side effects.

[0007] The foregoing examples of the related art and limitations related therewith are intended to be illustrative and not exclusive. Other limitations of the related art will become apparent to those of skill in the art upon a reading of the specification and a study of the figures.

SUMMARY

[0008] The following embodiments and aspects thereof are described and illustrated in conjunction with systems, tools and methods which are meant to be exemplary and illustrative, not limiting in scope.

[0009] There is provided, in accordance with an embodiment, a kit comprising: a urinary catheter comprising a first and a second longitudinal lumens; at least one ultrasonic transducer disposed about a distal portion of said urinary catheter; a balloon mounted on said urinary catheter at the distal portion, and enclosing said at least one ultrasonic transducer; and a reservoir containing an acoustic coupling medium, wherein: said urinary catheter further comprises a first opening in said first longitudinal lumen, said first opening disposed inside said balloon and configured to inflate said balloon with at least some of said acoustic coupling medium, said urinary catheter further comprises a second opening in said second longitudinal lumen, said second opening disposed outside said balloon and configured to deliver a therapeutic fluid into the urinary bladder, around said balloon, and activation of said at least one ultrasonic transducer in said urinary bladder causes cavitation bubbles to form in said therapeutic fluid adjacent an internal surface of the urinary bladder, and little or no cavitation bubbles are formed in said acoustic coupling medium in said balloon.

[0010] There is provided, in accordance with another embodiment, a method for delivering a therapeutic fluid to the urinary bladder, the method comprising: inserting a distal portion of a urinary catheter and at least one ultrasonic transducer disposed thereabout into said urinary bladder, wherein said at least one ultrasonic transducer is enclosed by a balloon, inflating said balloon with an acoustic coupling medium via a first longitudinal lumen and a first opening of said urinary catheter, wherein said first opening is disposed in said first longitudinal lumen and inside said balloon, delivering to said urinary bladder, around said balloon, therapeutic fluid via a second longitudinal lumen and a second opening of said urinary catheter, wherein said second opening is disposed in said second longitudinal lumen and outside said balloon, and activating said at least one ultrasonic transducer to transmit ultrasonic waves towards an internal surface of said urinary bladder, to form

cavitation bubbles in said therapeutic fluid adjacent to said internal surface and little or no cavitation bubbles in said acoustic coupling medium in said balloon.

[0011] There is provided, in accordance with a further embodiment, a device comprising: a urinary catheter comprising a first and a second longitudinal lumens; at least one ultrasonic transducer disposed about a distal portion of said urinary catheter; and a balloon mounted on said urinary catheter at the distal portion, and enclosing said at least one ultrasonic transducer; wherein: said urinary catheter further comprises a first opening in said first longitudinal lumen, said first opening disposed inside said balloon and configured to inflate said balloon with an acoustic coupling medium, said urinary catheter further comprises a second opening in said second longitudinal lumen, said second opening disposed outside said balloon and configured to deliver a therapeutic fluid into the urinary bladder, around said balloon, and activation of said at least one ultrasonic transducer in said urinary bladder causes cavitation bubbles to form in said therapeutic fluid adjacent an internal surface of the urinary bladder, and little or no cavitation bubbles are formed in said acoustic coupling medium in said balloon.

[0012] In some embodiments, the kit further comprises a reservoir containing said therapeutic fluid.

[0013] In some embodiments, the device and/or kit further comprise a cavitation monitor, wherein said cavitation monitor acquires acoustic emissions signals and transmits a digital signal. In some embodiments, the cavitation monitor comprises transducer detector disposed within said balloon. In some embodiments, the transducer detector is mounted on a distal portion of said urinary catheter.

[0014] In some embodiments, said therapeutic fluid comprises a cavitation booster selected from the group consisting of: an ultrasound contrast agent, micro-particles, nano-particles, liposomes, and a gas.

[0015] In some embodiments, said therapeutic fluid comprises one or more therapeutic agents selected from the group consisting of: a drug, a chemotherapeutic agent, a tracer, a marker, a radioactive compound, a small molecule, and a gene.

[0016] In some embodiments, said one or more therapeutic agents are selected from the group consisting of: anti muscarinic agents, anticholinergic agents, anesthetic agents, and botulinum toxins.

[0017] In some embodiments, said chemotherapeutic agent is selected from the group consisting of: Bacillus Calmette Guerin (BCG) vaccine, cisplatin, doxorubicin, valrubicin, gemcitabine, mycobacterial cell wall-DNA complex (MCC), methotrexate, vinblastine, thiotepa, mitomycin, fluorouracil, leuprolide, diethylstilbestrol, estramustine, megestrol acetate, cyproterone, flutamide, a selective estrogen receptor modulators (i.e. a SERM, such as tamoxifen), botulinum toxins, and cyclophosphamide.

[0018] In some embodiments, said at least one ultrasonic transducer is structured to produce an unfocused, diverging acoustic field.

[0019] In some embodiments, said at least one ultrasonic transducer is at least one tubular transducer surrounding a section of said urinary catheter.

[0020] In some embodiments, said at least one ultrasonic transducer is a flat, rectangular transducer.

[0021] In some embodiments, said urinary catheter further comprises a third longitudinal lumen and a third opening disposed inside said balloon, to allow circulating said at least some of said acoustic coupling medium in and out of said balloon, thereby cooling said at least some of said acoustic coupling medium.

[0022] In some embodiments, the kit further comprises a rotation unit configured to rotate at least said at least one ultrasonic transducer when said at least one ultrasonic transducer is activated.

[0023] In some embodiments, the balloon is shaped similarly to the shape of the urinary bladder and is smaller in size than the urinary bladder.

[0024] In some embodiments, the device and/or kit further comprise one or more spacers disposed on an external surface of said balloon.

[0025] In some embodiments, the device and/or kit further comprise a net surrounding said balloon.

[0026] In some embodiments, the balloon comprises a rough external surface.

[0027] In some embodiments, said at least one ultrasonic transducer is configured to resonate at a frequency between 36 Kilohertz and 550 Kilohertz.

[0028] In some embodiments, said at least one ultrasonic transducer is configured to resonate at a frequency between 36 Kilohertz and 100 Kilohertz. In some embodiments, said at least one ultrasonic transducer is configured to resonate at a frequency between 50 Kilohertz and 100 Kilohertz.

[0029] In some embodiments, said at least one ultrasonic transducer is configured to resonate at a frequency between 36 Kilohertz and one Megahertz and at a frequency above one Megahertz.

[0030] In some embodiments, said at least one ultrasonic transducer is a plurality of flat, rectangular transducers arranged around a section of said urinary catheter.

[0031] In some embodiments, said urinary catheter further comprises a third longitudinal lumen and a third opening disposed inside said balloon, and wherein said method further comprises circulating said at least some of said acoustic coupling medium in and out of said balloon via said first and third longitudinal lumens to cool said at least some of said acoustic coupling medium.

[0032] In some embodiments, the method further comprises rotating at least said at least one ultrasonic transducer when said at least one ultrasonic transducer is activated.

[0033] In some embodiments, the method further comprises rotating said urinary catheter.

[0034] In some embodiments, the method further comprises iteratively activating said at least one ultrasonic transducer and each time said urinary catheter is rotated.

[0035] In addition to the exemplary aspects and embodiments described above, further aspects and embodiments will become apparent by reference to the figures and by study of the following detailed description.

BRIEF DESCRIPTION OF THE FIGURES

[0036] Exemplary embodiments are illustrated in referenced figures. Dimensions of components and features shown in the figures are generally chosen for convenience and clarity of presentation and are not necessarily shown to scale. The figures are listed below.

[0037] Fig. 1 shows a top view and partially transparent of an exemplary device disposed within a urinary bladder, according to an embodiment;

[0038] Fig. 2A shows a side view and partially exploded of a distal portion of an exemplary urinary catheter, which incorporates a flat rectangular ultrasonic transducer, according to another embodiment;

[0039] Fig. 2B shows a top view of the flat rectangular ultrasonic transducer of Fig. 2A;

[0040] Fig 3 shows a perspective view of an exemplary device according to another embodiment;

[0041] Fig. 4 shows a top view and partially transparent of an exemplary device disposed within a urinary bladder, according to another embodiment;

[0042] Fig 5A shows a perspective view of the device of Fig. 1, according to another embodiment;

[0043] Fig. 5B shows a top view and partially transparent of the device of Fig. 5A disposed within a urinary bladder, according to an embodiment;

[0044] Fig. 6 shows a perspective view of an exemplary device according to a further embodiment;

[0045] Fig. 7 shows a perspective view of an exemplary device according to yet another embodiment;

[0046] Fig. 8 shows a top view and partially transparent of an exemplary system including a device disposed within a urinary bladder, according to an embodiment;

[0047] Fig. 9 shows a top view and partially transparent of an exemplary implementation of the system of Fig. 8, in accordance with another embodiment;

[0048] Fig. 10A is a graph showing a change in spectrum as a function of acoustic emission frequency;

[0049] Fig. 10B is a graph showing a change of voltage as a function of time in a weak cavitation processes versus strong cavitation processes;

[0050] Fig. 10C is a graph showing a change of the square of a voltage as a function of time $V^2(t)$ in weak cavitation processes and strong cavitation processes;

[0051] Fig 11A shows a top view and partially transparent of an exemplary implementation of the system of Fig. 9, in accordance with another embodiment;

[0052] Fig 11B is a schematic view showing emitting surface of an ultrasound transducer, in accordance with an embodiment;

[0053] Fig 12 shows a top view and partially transparent of an exemplary implementation of the system of Fig. 9, in accordance with another embodiment;

[0054] Fig 13 shows a top view and partially transparent of an exemplary implementation of the system of Fig. 9, in accordance with another embodiment;

[0055] Fig. 14 shows a flowchart of a method for delivering a therapeutic fluid to a urinary bladder, constructed and operative in accordance with an embodiment of the disclosed technique;

[0056] Fig. 15A shows the device of Fig.1 when inserted into the urinary bladder, according to the method of Fig. 14;

[0057] Fig. 15B shows the device of Fig.1 when inflated within the urinary bladder and therapeutic fluid is introduced to the urinary bladder, according to the method of Fig. 14; and

[0058] Fig. 15C shows the device of Fig.1 when ultrasonic waves are applied to the urinary bladder and cavitation of the therapeutic fluid is formed, according to the method of Fig. 14.

DETAILED DESCRIPTION

[0059] The disclosed device, kit and method may increase the permeability of the urinary bladder (or simply 'bladder') tissue and/or prostate tissue to therapeutic agents such as drugs. By allowing the delivery of higher drug concentration, for example, into bladder internal surface and into deeper layers of the bladder wall, improvement of standard intravesical bladder therapy may be achieved. A skilled artisan will appreciate the advantage of utilizing the device of the instant invention for drug (e.g., Botox) delivery, such as to the bladder wall, over common methods which include multiple injections of the drugs to the bladder wall. The disclosed device, kit and method are based on the application of ultrasound to the bladder tissue and/or to a therapeutic agent adjacent to the bladder internal surface. Ultrasound may increase permeability through thermal and/or cavitation mechanisms. The disclosed device, kit and method may utilize one or both mechanisms in order to improve the delivery of therapeutic agents into bladder tissue. The disclosed device, kit and method further deliver a therapeutic agent, a drug, marker, a radioactive molecule, a chemotherapeutic compound or any combination thereof. The disclosed device, kit and method further enhance and/or facilitate the in-situ delivery of a therapeutic agent, a drug, marker, a radioactive molecule, a chemotherapeutic compound or any combination thereof into a target tissue such as but not limited to the: bladder or urethra and/or prostate. The disclosed device, kit and method further enhance the permeability of a target tissue thus enhancing in-situ delivery of a therapeutic agent into the target tissue and/or a bladder.

[0060] In general, under ultrasound irradiation of the bladder, cavitation bubbles may form anywhere in the fluid contained in the bladder. Moreover, in the case that an ultrasound transducer applies ultrasound from within the bladder, cavitation bubbles may form on the transducer itself, or near the transducer's surface, often blocking ultrasound energy from reaching the bladder wall. Even at low bladder volumes, the bladder wall may be up to four centimeters distant from the center of the bladder. Hence, it may be unlikely to produce cavitation only or substantially near the internal surface of the bladder (i.e., and not near the surface of the transducer) from an ultrasound transducer radiating from a centralized position in the bladder.

[0061] The disclosed device, kit and method may allow controlling of the cavitation formation and location. Cavitation bubbles may be formed near the bladder internal surface, in order to increase the delivery of therapeutic agents. Furthermore, cavitation may be prevented or substantially prevented from forming near the ultrasonic transducer and from blocking ultrasound energy (also called a “shielding effect”) from reaching bladder wall. Cavitation bubbles may be formed near the bladder internal surface without the need to mount the ultrasonic transducer (or simply 'transducer') very close to the bladder internal surface (e.g., in a distance of less than one centimeter or even in contact with the internal surface). As a result, in some embodiments of the disclosed device, kit and method, the transducer may be distant from the bladder internal surface. For example, the transducer may be mounted in a position which is distant by up to 8 centimeters (cm) from the bladder internal surface, and in some embodiments even more.

[0062] The control of cavitation formation and location may be achieved by enclosing the transducer with a balloon filled with an acoustic coupling medium which does not favor cavitation, such as a degassed solution. In such a solution, cavitation may not form or substantially may not form. Hence, the one or more transducers (which may be disposed, for example, on a urinary catheter and inside the balloon) may be immersed in an acoustic coupling medium, and cavitation may not form on or near the transducers. Thus, cavitation may not block ultrasound energy directed to bladder.

[0063] In order to form cavitation near the bladder internal surface, cavitation may be formed in a therapeutic fluid that interacts with the bladder. In one non-limiting example, the therapeutic fluid may include the therapeutic agent to be delivered to the bladder and is introduced to the cavity between the balloon and the bladder internal surface. In yet another example, the therapeutic agent may be introduced to the therapeutic fluid following the application of ultrasonic radiation (e.g., 1-2 hours following the operation of the ultrasound transducers).

[0064] This therapeutic fluid may allow the formation of cavitation under ultrasound which may increase bladder permeability. Optionally, the ultrasound waves pushes the therapeutic agent into the bladder wall. In order to encourage cavitation in the therapeutic fluid, its gas content may be increased. Alternatively, cavitation boosters (i.e., a cavitation

favoring agents) may be added to the therapeutic fluid. Non-limiting examples of cavitation boosters include ultrasound contrast agents, such as microbubbles (e.g., Definity®, Optison® and SonoVue®), micro-particles, nano-particles, or liposomes. In this manner, the intensity levels needed to form cavitation may be decreased. In some embodiments, the therapeutic agents may be encapsulated in the cavitation boosters, which may result in a more efficient delivery of the therapeutic agent to the bladder wall.

[0065] Optionally, when the ultrasound transducers are external ultrasound transducers, the balloon may be filled with gas (e.g., air, argon, etc.) and the cavity between the balloon and the bladder internal surface may be filled with a therapeutic fluid with decreased cavitation threshold (e.g., supplemented with microbubbles, micro-particles, nano-particles, and/or liposomes). Thus, when the external ultrasound transducers are utilized, acoustic energy reflects and bends around a surface of the balloon, rather than penetrate the balloon. When the external ultrasound transducers are utilized, acoustic pressure may increase in the therapeutic fluid and at some level of acoustic pressure the cavitation in the layer between the balloon surface and the bladder surface will be initiated.

[0066] In some embodiments, the balloon is filled with a fluid. Optionally, the balloon comprises an aqueous solution. Optionally, the balloon comprises a gel or a viscous liquid. Optionally, the viscous liquid has a viscosity of at least 1.0020mPa·s at 20 °C. Optionally, the viscous liquid has a viscosity of at least 1.1mPa·s, 1.2mPa·s, 1.3mPa·s, 1.4mPa·s, 1.5mPa·s, 1.6mPa·s, 1.7mPa·s, 1.8mPa·s, 1.9mPa·s, 2mPa·s, 2.2mPa·s, 2.4mPa·s, 2.6mPa·s, 3mPa·s, or 3.5mPa·s. Optionally, viscosity is dynamic viscosity.

[0067] The balloon may be made of a wide variety of materials including, for example, polytetrafluoroethylenes (Teflon®), polyethylenes, (e.g., high density polyethylenes), polyethylene terephthalate (PET), polypropylenes, polyurethanes, nylons including nylon 6 and nylon 12, polyesters including polyalkylene terephthalate polymers and copolymers, (e.g., thermoplastic polyester elastomers such as Hytrel®, which is a block copolymer containing a hard polybutylene terephthalate segment and soft amorphous segments based on long-chain polyether glycols), polyimides, polyamides including polyether-block-copolyamide polymers (e.g., Pebax®), and the like. These materials may also be blended or

provided in a composite or multi-layer construction. Typically, PET balloons are substantially optically clear and permit the transmission of light over a broad spectrum.

[0068] Optionally, an outer surface of the balloon which interacts with the therapeutic fluid may be configured to trap cavitation nuclei (seeds) and increase cavitation phenomenon in the therapeutic fluid (e.g., a rough outer surface). As used herein, the term "rough outer surface" refers to a surface having multi-faceted symmetrical or non-symmetrical features containing points, ridges and multifaceted edges and angles. A roughness value may be calculated on a profile (line). For example, Ra is the arithmetic average of the absolute values of the profile height deviations from the mean line, and its value is expressed in micrometers (μm). Optionally, the "rough outer surface" may have an Ra value of 10 to 100 μm , 100 to 200 μm , 200 to 300 μm , 300 to 400 μm , 400 to 500 μm , 500 to 600 μm , 600 to 700 μm , 700 to 800 μm , 800 to 900 μm , or 900 to 1000 μm . Alternatively, the balloon may be covered with a net or a mesh which traps cavitation seeds and encourages cavitation.

[0069] In addition, the disclosed device, kit and method may allow pushing molecules of a therapeutic agent towards the bladder internal surface. In standard practice, the bladder may be filled with therapeutic fluid, and the molecules of the therapeutic fluid (i.e., including the molecules of the therapeutic agent, if included or when added) float in the fluid found in the entire bladder space. Thus, only a small fraction of the total number of the therapeutic agent molecules may come in contact with the bladder lining. Ultrasound cavitation phenomenon near bladder internal surface, such as streaming and micro-steaming, may push the therapeutic agent into the bladder internal surface. Hence, forming cavitation near the bladder wall may effectively increase the fraction of therapeutic agent molecules that interact with the bladder lining.

[0070] The term "**cavitation**", as referred to herein, may relate to the formation and collapse of cavities (bubbles) in a liquid which undergoes a rapid pressure fluctuation generated by an acoustic source (e.g., ultrasound). Reference is often made to two types of ultrasound induced cavitation, referred to as inertial and stable cavitation. **Inertial cavitation** is characterized by bubbles which grow and implode violently within a few cycles of excitation, collapsing bubbles produce shock waves characterized by wide-band

acoustic spectra, up to 15-20 Megahertz (MHz). During cavitation event, many bubbles implode thus a resulting acoustic signal would be observed as a random noise having a wide spectrum up to 20 MHz or even wider. **Stable cavitation** is characterized by bubbles which sustain and repetitively oscillate for a longer period of time. The acoustic emission is characterized by harmonics and sub-harmonics of the operational frequency (f_0) of the High-Intensity Ultrasound Transducer ("HIUT"). The most prominent ones are $f_0/2$, $2f_0$, $3f_0$, $3f_0/2$ and $5f_0/2$, the last two are called ultraharmonics. All these signals may be monitored by an acousto-electric sensor, which converts acoustic pressure into electric signals. The most common type of such sensor is a piezoelectric transducer. Methods for cavitation monitoring are well known in the art, a main quantitative technique for cavitation detection and measurement is passive cavitation detection, which exploits the acoustic emissions generated by cavitating bubbles. Passive techniques use ultrasound transducers, which may have different shapes, usually focused or planar, called a Passive Cavitation Detector (PCD), to acquire acoustic emissions signals resulting from cavitation. Passive cavitation detection can be easily implemented and has been widely used over a range of applications.

[0071] The term "**therapeutic agent**", as referred to herein, may relate to any therapeutic substance, such as a drug (e.g., Botox), a chemotherapeutic agent, a tracer, a marker, a radioactive compound, a small molecule, or a gene.

[0072] The term "**therapeutic fluid**", as referred to herein, may relate to a fluid, which includes a therapeutic agent or designated to be added with the therapeutic agent following the application of ultrasonic radiation. The therapeutic fluid may be, for example, a solution, where the solute is the therapeutic agent and the solvent may be, for example, saline, ethanol, water or acetic acid. Accordingly, in some embodiments, the therapeutic fluid may at first include only the solvent, and later it may be added with the therapeutic agent. In some embodiments, a "therapeutic fluid" comprises a probing agent which binds, adheres or marks/identifies a specific tissue or a cell type such as but not limited to a cancerous cell. In some embodiments, a probing agent is a labeled compound. In some embodiments, a probing agent is a radioactive compound. In some embodiments, a probing agent is a fluorescently labeled compound.

[0073] The terms "**tissue**" and "**wall**", as referred to herein with respect to a urinary bladder, may relate to the tissue forming the urinary bladder, and may be used interchangeably. The term "**internal surface**", as referred to herein with respect to the urinary bladder, may relate to the internal surface of such wall or tissue of the bladder. These terms may relate to the entire and/or to a portion of the bladder, according to their context.

[0074] The term "**acoustic coupling medium** ", as referred to herein, may relate to a medium which allows efficient progression of ultrasound energy. An important aspect of this medium is that it does not favor cavitation phenomenon, which may block ultrasound energy from progressing from the transducer to the bladder internal surface. Such medium may be degassed (i.e., its gases were removed), e.g., degassed solution such as saline which went through boiling, or a solution which its gas content was filtered out.

[0075] The chemotherapeutic agent is, in some embodiments, a bladder chemotherapeutic agent. The drug, in some embodiments, is an intra-bladder medicament. The therapeutic agent is, in some embodiments, botulinum toxin or onabotulinumtoxinA (also known as Botox). The therapeutic agent is, in some embodiments, an overactive bladder medicament. The therapeutic agent is, in some embodiments, an anti-muscarinic agent, an anticholinergic agent or a combination thereof. The therapeutic agent is, in some embodiments, an anesthetic agent. In some embodiments, overactive bladder includes urinary urgency, frequency and nocturia, and incontinence.

[0076] In some embodiments, the therapeutic agent or drug is any therapeutic, prophylactic, or diagnostic agent, such as one that would be useful to release locally into the prostate, bladder, or ureter for local or regionally treatments. The kit, methods and device of the invention enhance and/or facilitate the in-situ delivery of the therapeutic agent compared to traditional delivery methods such as site specific injection or systemic delivery. Delivery may be in a faster and/or more uniform manner. Optionally, higher concentration of the therapeutic drugs may be delivered compared to traditional delivery methods. Optionally, delivery to deeper layer of the bladder wall may be facilitated, compared to traditional delivery methods. The kit, methods and device of the invention enhance and/or facilitate the in-situ delivery of the therapeutic agent into the bladder or the urethra, compared to traditional delivery methods such as site specific injection or systemic delivery.

The kit, methods and device of the invention, in some embodiments, reduce side effects resulting from the compounds and the traditional delivery methods such as site specific injection or systemic delivery. In some embodiments, the "therapeutic agent" or "drug" comprises one or more pharmaceutically acceptable excipients. The drug may be a biologic. The drug may be a metabolite. As used herein, the term "drug" with reference to any specific drug described herein includes its alternative forms, such as salt forms, free acid forms, free base forms, solvates, and hydrates. Pharmaceutically acceptable excipients are known in the art and may include lubricants, viscosity modifiers, surface active agents, osmotic agents, diluents, and other non-active ingredients of the formulation intended to facilitate handling, stability, dispersibility, wettability, and/or release kinetics of the drug.

[0077] The kit, methods and device of the invention is used, according to some embodiments, for treating pain. In some embodiments, the therapeutic agent or drug is an analgesic agent. In some embodiments, the therapeutic agent or drug is a cocaine analogue. In some embodiments, the therapeutic agent or drug is an aminoamide. In some embodiments, the therapeutic agent or drug is an aminoester or ester-class anesthetic. In some embodiments, the therapeutic agent or drug is lontocaine. In some embodiments, the therapeutic agent or drug is oxybutynin or propiverine.

[0078] In some embodiments, the therapeutic agent or drug is an opioid or an opioid agonist such as but not limited to: alfentanil, allylprodine, alphaprodine, anileridine, benzylmorphine, bezitramide, buprenorphine, butorphanol, clonitazene, codeine, desomorphine, dextromoramide, dezocine, diampromide, diamorphone, dihydrocodeine, dihydromorphine, dimenoxadol, dimepheptanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, eptazocine, ethoheptazine, ethylmethylthiambutene, ethylmorphine, etonitazene, fentanyl, heroin, hydrocodone, hydromorphone, hydroxypethidine, isomethadone, ketobemidone, levorphanol, levophenacymorphan, lofentanil, meperidine, meptazinol, metazocine, methadone, metopon, morphine, myrophine, nalbuphine, narceine, nicomorphine, norlevorphanol, normethadone, nalorphine, normorphine, norpipanone, opium, oxycodone, oxymorphone, papaveretum, pentazocine, phenadoxone, phenomorphan, phenazocine, phenoperidine, piminodine, piritramide, proheptazine, promedol, properidine, propiram, propoxyphene, sufentanil, tilidine, tramadol,

pharmaceutically acceptable salts thereof, and mixtures thereof. In some embodiments, the therapeutic agent or drug is a mu, kappa, delta, or nociception opioid receptor agonists.

[0079] In some embodiments, the therapeutic agent or drug is an analgesic such as but not limited to: acetaminophen, buprenorphine, butorphanol, codeine, dihydrocodeine, fentanyl, heroin, hydrocodone, hydromorphone, methadone, morphine, nicomorphine, oxycodone, oxymorphone, pentazocine, pethidine, propoxyphene, pyridium (phenazopyridine), thebaine, tramadol, alicyl alcohol, phenazopyridine hydrochloride, acetylsalicylic acid, flufenisal, ibuprofen, indoprofen, indomethacin, naproxen, or any combination thereof.

[0080] In some embodiments, the device, kit and methods are utilized for treating an inflammatory condition or inflammation. In some embodiments, the device, kit and methods are utilized for treating radiation cystitis, prostatitis, urethritis, post-surgical pain, or kidney stones. In some embodiments, the therapeutic agent or drug is: lidocaine, glycosaminoglycans (e.g., chondroitin sulfate, sulodexide), pentosan polysulfate sodium (PPS), dimethyl sulfoxide (DMSO), oxybutynin, mitomycin C, heparin, flavoxate, ketorolac, or a combination thereof. In some embodiments, the therapeutic agent or drug is Tanezumab or a channel alpha-2-delta modulator (such as PD-299685 or gabapentin).

[0081] In some embodiments, the device, kit and methods are utilized for the placement of a ureteral stent, such as to treat pain, urinary urgency or urinary frequency resulting from ureteral stent placement. Non-limiting examples of specific drugs for such treatment include anti- muscarinics, a-blockers, narcotics, and phenazopyridine, among others.

[0082] In some embodiments, the device, kit and methods are utilized for treating urinary incontinence, frequency, or urgency, including urge incontinence and neurogenic incontinence, as well as trigonitis. Drugs that may be used include anticholinergic agents, antispasmodic agents, anti- muscarinic agents, β -2 agonists, alpha adrenergics, anticonvulsants, norepinephrine uptake inhibitors, serotonin uptake inhibitors, calcium channel blockers, potassium channel openers, and muscle relaxants. Representative examples of suitable drugs for the treatment of incontinence include oxybutynin, S-oxybutytin, emepronium, verapamil, imipramine, flavoxate, atropine, propantheline, tolterodine, rociverine, clenbuterol, darifenacin, terodiline, trospium, hyoscyamin, propiverine, desmopressin, vamicamide, clidinium bromide, dicyclomine HCl,

glycopyrrolate aminoalcohol ester, ipratropium bromide, mepenzolate bromide, methscopolamine bromide, scopolamine hydrobromide, iotropium bromide, fesoterodine fumarate, YM-46303 (Yamanouchi Co., Japan), lanperisone (Nippon Kayaku Co., Japan), inaperisone, NS-21 (Nippon Shinyaku Orion, Formenti, Japan/Italy), NC-1800 (Nippon Chemiphar Co., Japan), Z D-6169 (Zeneca Co., United Kingdom), and stilonium iodide.

[0083] In some embodiments, the device, kit and methods are utilized for treating urinary tract cancer, such as bladder cancer and prostate cancer. Drugs that may be used include antiproliferative agents, cytotoxic agents, chemotherapeutic agents, or a combination thereof. Representative examples of drugs which may be suitable for the treatment of urinary tract cancer include Bacillus Calmette Guerin (BCG) vaccine, cisplatin, doxorubicin, valrubicin, gemcitabine, mycobacterial cell wall-DNA complex (MCC), methotrexate, vinblastine, thiotepa, mitomycin, fluorouracil, leuprolide, diethylstilbestrol, estramustine, megestrol acetate, cyproterone, flutamide, a selective estrogen receptor modulators (i.e. a SERM, such as tamoxifen), botulinum toxins, and cyclophosphamide. The drug may be a biologic, and it may comprise a monoclonal antibody, a TNF inhibitor, an anti-leukin, or the like. The drug also may be an immunomodulator, such as a TLR agonist, including imiquimod or another TLR7 agonist. The drug also may be a kinase inhibitor, such as a fibroblast growth factor receptor-3 (FGFR3)-selective tyrosine kinase inhibitor, a phosphatidylinositol 3 kinase (PI3K) inhibitor, or a mitogen-activated protein kinase (MAPK) inhibitor, among others or combinations thereof. Other examples include celecoxib, erlotinib, gefitinib, paclitaxel, polyphenon E, valrubicin, neocarzinostatin, apaziquone, Belinostat, Ingenol mebutate, Urocidin (MCC), Proxinium (VB 4845), BC 819 (BioCancell Therapeutics), Keyhole limpet haemocyanin, LOR 2040 (Lorus Therapeutics), urocanic acid, OGX 427 (OncoGenex), and SCH 721015 (Schering-Plough). Other intravesical cancer treatments include small molecules, such as Apaziquone, adriamycin, AD-32, doxorubicin, doxetaxel, epirubicin, gemcitabine, HTI-286 (hemiasterlin analogue), idarubicin, γ -linolenic acid, mitozantrone, meglumine, and thiotepa; large molecules, such as Activated macrophages, activated T cells, EGF-dextran, HPC-doxorubicin, IL-12, IFN- α 2b, IFN- γ , α -lactalbumin, p53 adenovector, TNF α ; combinations, such as Epirubicin + BCG, IFN + farmarubicin, Doxorubicin + 5-FU (oral), BCG + IFN, and Pertussis toxin + cystectomy; activated cells, such as macrophages and T cells; intravesical infusions such as

IL-2 and Doxorubicin; chemosensitizers, such as BCG+antifibrinolytics (paramethylbenzoic acid or aminocaproic acid) and Doxorubicin + verapamil; diagnostic/imaging agents, such as Hexylaminolevulinate, 5 -aminolevulinic acid, Iododexyuridine, HMFG1 Mab+Tc99m; and agents for the management of local toxicity, such as Formaline (hemorrhagic cystitis).

[0084] In some embodiments, the device, kit and methods are utilized for treating infections involving the bladder, the prostate, and the urethra. In some embodiments, the drug is an antibiotics, an antibacterial, an antifungal, an antiprotozoal, an antiseptic, an antiviral or any other anti-infective agent.

[0085] In some embodiments, the therapeutic agent or drug is mitomycin, ciprofloxacin, norfloxacin, ofloxacin, methanamine, nitrofurantoin, ampicillin, amoxicillin, nafcillin, trimethoprim, sulfonamides trimethoprim-sulfamethoxazole, erythromycin, doxycycline, metronidazole, tetracycline, kanamycin, penicillins, cephalosporins, or an aminoglycoside.

[0086] In some embodiments, the device, kit and methods are utilized for treating fibrosis of a genitourinary site, such as but not limited to the bladder or uterus. In some embodiments, the device, kit and methods are utilized for treating a neurogenic bladder. In some embodiments, the therapeutic agent or drug is pentoxifylline (xanthine analogue), an anti-TNF-agent, an anti-TGF agents, a GnRH analogue, an exogenous progestin, an antiprogestins, a selective estrogen receptor modulator, danazol, a NSAID, or any combination thereof. In some embodiments, the therapeutic agent or drug is a known drug for the treatment of incontinence due to neurologic detrusor overactivity and/or low compliant detrusor. Examples of these types of drugs include bladder relaxant drugs (e.g., oxybutynin (antimuscarinic agent with a pronounced muscle relaxant activity and local anesthetic activity), propiverine, ipratropium, tiotropium, trospium, terodiline, tolterodine, propantheline, oxyphenacyclimine, flavoxate, and tricyclic antidepressants; drugs for blocking nerves innervating the bladder and urethra (e.g., vanilloids (capsaicin, resiniferatoxin), botulinum- A toxin); or drugs that modulate detrusor contraction strength, micturition reflex, detrusor sphincter dyssynergia (e.g., GABA_B agonists (baclofen), benzodiazepines). In another embodiment, the drug is selected from those known for the treatment of incontinence due to neurologic sphincter deficiency. Examples of these drugs include alpha adrenergic agonists, estrogens, beta-adrenergic agonists, tricyclic

antidepressants (imipramine, amitriptyline). In still another embodiment, the drug is selected from those known for facilitating bladder emptying (e.g., alpha adrenergic antagonists (phentolamine) or cholinergics). In yet another embodiment, the drug is selected from among anticholinergic drugs (e.g., dicyclomine), calcium channel blockers (e.g., verapamil) tropane alkaloids (e.g., atropine, scopolamine), nociceptin/orphanin FQ, and bethanechol (e.g., m3 muscarinic agonist, choline ester).

[0087] In some embodiments, the therapeutic agent or drug is oxybutynin. In some embodiments, the therapeutic agent or drug is a β -3 adrenergic receptor (β 3-AR) agonist. In another embodiment, the therapeutic agent or drug is oxybutynin. In another embodiment, the therapeutic agent or drug is Tolterodine tartrate. In another embodiment, the therapeutic agent or drug is Fesoterodine fumarate. In another embodiment, the therapeutic agent or drug is Solifenacin. In another embodiment, the therapeutic agent or drug is Trospium chloride. In another embodiment, the therapeutic agent or drug is Darifenacin. In another embodiment, the therapeutic agent or drug is Propiverine. In another embodiment, the therapeutic agent or drug is a Tricyclic antidepressant. In another embodiment, the therapeutic agent or drug is Desmopressin. In another embodiment, the therapeutic agent or drug is an estrogen therapeutic agent.

[0088] In some embodiments, a drug or an agent as described herein is within a "therapeutic fluid". In some embodiments, a "therapeutic fluid" is a pharmaceutical composition. In some embodiments, a "therapeutic fluid" is a liquid pharmaceutical composition. In some embodiments, a "therapeutic fluid" is an aqueous pharmaceutical composition.

[0089] In some embodiments, the present invention provides a superior in vivo delivery system for a compound to be delivered into a bladder tissue. In some embodiments, the present invention provides an enhanced dispersion of a compound to be delivered into a bladder tissue. In some embodiments, the present invention provides enhanced and deeper tissue penetration of a compound to be delivered into a bladder tissue. In some embodiments, the present invention provides a faster in vivo delivery system that is capable of delivering to a compound to be delivered into a bladder tissue. In some embodiments, the kit and/or system as described herein increases and/or enhances the area under the curve

(AUC) measure of a compound present within the therapeutic fluid. In some embodiments, the kit and/or system as described herein reduces the half time ($t_{1/2}$) measure of a compound present within the therapeutic fluid. In some embodiments, the kit and/or system as described herein increases and/or enhances the C_{max} measure of a compound present within the therapeutic fluid. In some embodiments, the kit and/or system as described herein increases and/or enhances the V_{max} measure of a compound present within the therapeutic fluid.

[0090] In some embodiments, the present invention reduces the risk of (a) long-term increase in tissue permeability and/or (b) long-term decrease tissue integrity within a bladder, due to the delivery of a therapeutic fluid with the systems and kits as described herein. In some embodiments, the risk of increase in tissue permeability and decrease in tissue integrity is apparent days, weeks or months after a procedure such as described herein, is performed. In some embodiments, the present invention provides efficient means (the kits and systems) for penetration and delivery of a therapeutic agent into a bladder without causing prolonged and/or terminal damage to the bladder tissue. In some embodiments, the present invention provides efficient means (the kits and systems) for reducing nonspecific delivery of a therapeutic agent into a bladder tissue.

[0091] In some embodiments, the present invention provides that at least 30% of the therapeutic compound/drug or therapeutic fluid within the system and/or kit, penetrates and/or being absorbed within a bladder tissue. In some embodiments, the present invention provides that at least 40% of the therapeutic compound/drug or therapeutic fluid within the system and/or kit, penetrates and/or being absorbed within a bladder tissue. In some embodiments, the present invention provides that at least 50% of the therapeutic compound/drug or therapeutic fluid within the system and/or kit, penetrates and/or being absorbed within a bladder tissue. In some embodiments, the present invention provides that at least 60% of the therapeutic compound/drug or therapeutic fluid within the system and/or kit, penetrates and/or being absorbed within a bladder tissue. In some embodiments, the present invention provides that at least 70% of the therapeutic compound/drug or therapeutic fluid within the system and/or kit, penetrates and/or being absorbed within a bladder tissue. In some embodiments, the present invention provides that at least 80% of the therapeutic compound/drug or therapeutic fluid within the system and/or kit, penetrates and/or being

absorbed within a bladder tissue. In some embodiments, the present invention provides that at least 85% of the therapeutic compound/drug or therapeutic fluid within the system and/or kit, penetrates and/or being absorbed within a bladder tissue. In some embodiments, the present invention provides that at least 90% of the therapeutic compound/drug or therapeutic fluid within the system and/or kit, penetrates and/or being absorbed within a bladder tissue.

[0092] In some embodiments, the present invention provides efficient means (the kits and systems) for local delivery of drugs directly into the bladder. In some embodiments, the present invention provides kits and systems which minimize systemic bioavailability of the delivered therapeutic agent or drug. In some embodiments, the present invention provides kits and systems ensuring minimal adverse toxicity.

[0093] In one embodiment, a device, kit and/or system as described herein continuously releases the therapeutic fluid. In one embodiment, a device, kit and/or system as described herein releases the therapeutic fluid into the urine in the bladder over a sustained period. In one embodiment, a device, kit and/or system as described herein releases fixed dosages of the therapeutic fluid in pulses over a sustained period. In one embodiment, a device, kit and/or system as described herein comprises a predefined release aperture. In one embodiment, a device, kit and/or system as described herein comprises a therapeutic fluid reservoir portion or chamber.

[0094] In one embodiment, a device, kit and/or system as described herein provides that the therapeutic agent is maintained within the target tissue/bladder for at least 1 hour. In one embodiment, a device, kit and/or system as described herein provides that the therapeutic agent is maintained within the target tissue/bladder for at least 2 hours. In one embodiment, a device, kit and/or system as described herein provides that the therapeutic agent is maintained within the target tissue/bladder for at least 2.5 hours. In one embodiment, a device, kit and/or system as described herein enables the retention of the therapeutic agent within the target tissue/bladder for at least 3 hours. In one embodiment, a device, kit and/or system as described herein provides prolonged exposure of the therapeutic agent/drug within the urothelium. In one embodiment, a device, kit and/or system as described herein enables the exposure of the therapeutic agent/drug within the urothelium beyond the first, second, and/or third voiding of urine

[0095] In some embodiments, a "therapeutic fluid" comprises liquid solutions, emulsions, suspensions, and the like. In some embodiments, pharmaceutically-acceptable carriers suitable for preparation of such compositions (therapeutic fluid) are well known in the art. In some embodiments, therapeutic fluid comprises from about 0.012% to about 0.933% of the desired compound drug or compounds/drugs, or in another embodiment, from about 0.033% to about 0.7%.

[0096] In some embodiments, therapeutic fluid for use in the methods, kits and devices of this invention comprise solutions or emulsions, which in some embodiments are aqueous solutions or emulsions comprising a safe and effective amount of the compounds of the present invention and optionally, other compounds. In some embodiments, the compositions comprise from about 0.01% to about 10.0% w/v of a subject compound or from about 0.1% to about 2.0.

[0097] In some embodiments, therapeutic fluid includes solutions, suspensions, dispersions, emulsions, oils and the like with or without a pharmaceutical carrier. In one embodiment, therapeutic fluid includes a compatible buffer such as Hank's solution, Ringer's solution, or physiological salt buffer. In some embodiments, therapeutic fluid includes a penetrant.

[0098] In some embodiments, the therapeutic fluid is in unit dosage form, e.g., in ampoules or in multidose containers with optionally, an added preservative. In some embodiments, the therapeutic fluid is a suspension, solution or emulsion in oily or aqueous vehicle, and comprise a formulatory agent such as suspending, stabilizing and/or dispersing agents.

[0099] In some embodiments, the therapeutic fluid comprises lipophilic solvents or vehicles such as but not limited to: fatty oils such as sesame oil, or synthetic fatty acid esters such as ethyl oleate, triglycerides or liposomes. In some embodiments, the therapeutic fluid comprises substances, which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol or dextran. In some embodiments, the therapeutic fluid comprises suitable stabilizers or agents which increase the solubility of the active ingredients (drug and/or agent) to allow for the preparation of highly concentrated solutions.

[00100] In some embodiments, the active ingredient or drug is in powder form for constitution with a suitable vehicle, e.g., sterile, pyrogen-free water based solution, before use. In some embodiments, the phrase "detrusor overactivity" is synonymous with the phrase "overactive bladder". In some embodiments, overactive bladder is idiopathic and/or neurogenic overactive bladder. In some embodiments, overactive bladder is a pediatric overactive bladder. The therapeutic agent is, in some embodiment, a blocker of post-synaptic muscarinic receptors on the detrusor muscle. In one embodiment, the therapeutic agent is mirabegron.

[00101] Reference is now made to Fig. 1, which shows a top view and partially transparent of an exemplary device **100** disposed within a urinary bladder **190** according to an embodiment. Device **100** may be configured such that it may be introduced into urinary bladder **190** (or simply 'bladder **190**'). Device **100** may include a urinary catheter **110** (or simply 'catheter **110**'), ultrasonic transducers **120** and a balloon **130**. Urinary catheter **110** may include a first longitudinal lumen (not shown), a second longitudinal lumen **140**, a first opening (not shown) and a second opening **150**. Device **100** may further include electrical wires **180**. Device **100** may be operatively coupled with a console **195** via electrical wires **180**. Console **195** may include a power source and a pump (not shown). Electrical wires **180** may operatively couple transducers **120** with the power supply of console **195**.

[00102] Catheter **110** may include a distal portion and a proximal portion with respect to an operator of catheter **110** (e.g., a physician). At least the distal portion may be configured to be inserted into bladder **190**. At least an end section of the proximal portion may be left outside of a patient's body and may be operatively coupled with console **195**. The first longitudinal lumen may extend from the end section of the proximal portion to the distal portion of catheter **110** and may be configured to receive an acoustic coupling medium (not shown). The first opening may be disposed in the first longitudinal lumen in the distal portion of catheter **110**. The first opening may be disposed inside balloon **130**. The first opening may be configured to inflate balloon **130** with at least some of the acoustic coupling medium. Second longitudinal lumen **140** may extend from the end section of the proximal portion to the distal portion of catheter **110** and may be configured to receive a therapeutic fluid (not shown) which may include a therapeutic agent **145** (shown as molecules). Second opening **150** may be disposed in second longitudinal lumen **140** in the distal portion of

catheter **110**. Second opening **150** may be disposed outside of balloon **130**. Second opening **150** may be configured to deliver the therapeutic fluid (i.e., therapeutic agent **145**) into bladder **190**, around balloon **130**.

[00103] Urinary catheter **110** may include a main channel **170**. Catheter **110** may further include an inlet channel **160** and an outlet channel **165**. One of inlet channels **160** or **165** may be the first longitudinal lumen and may include the first opening while the other may be a third longitudinal lumen and may include a third opening disposed inside balloon **130** (not shown). Inlet channel **160** may be configured to introduce the acoustic coupling medium to balloon **130**. Outlet channel **165** may be configured to evacuate the acoustic coupling medium from balloon **130**. Main channel **170** may include several separate channels (not shown). Main channel **170** may include a drug irrigation channel, which may be second longitudinal lumen **140**. Main channel **170** may further include a channel along which electrical wires **180** may run (not shown). Electrical wires may operatively couple ultrasonic transducers **120** with the power supply of console **195**.

[00104] In some embodiments, urinary catheter **110** may include three channels. In some embodiments, urinary catheter **110** may include a first main channel configured to drain the bladder and deliver drug to it; a second channel configured to allow passage of the electrical wires; and a third channel configured to allow inflation and deflation of the balloon. In some embodiments, urinary catheter **110** may include a first main channel configured to drain the bladder and deliver drug to it and to allow passage of the electrical wires; a second and a third channel configured to allow circulation of a cooled acoustic coupling medium through the balloon. In some embodiments, urinary catheter **110** may include a first and a second channel configured to circulate therapeutic fluid in the bladder; and a third channel configured to inflate and deflate the balloon. In some embodiments, urinary catheter **110** may include four channels. Such embodiments may include the three channels of the three channel embodiments, as described above, and a fourth channel configured and dedicated to allow passage of the electrical wires.

[00105] In some embodiment catheter **110** may be a known catheter such as a standard Foley catheter. Alternatively, the diameter and length of catheter **110** may be similar to those of a standard Foley catheter. Optionally, the length of catheter **110** may range from 5

to 50 millimeters. In some embodiments, the diameter of catheter **110** may vary along its length, in order to accommodate the mounting of ultrasonic transducers **120**.

[00106] Following the insertion of catheter **110** into bladder **190**, a tip of the distal portion of catheter **110** may bend downwards due to gravity. In order to achieve a uniform Ultrasound coverage of the inner surface of bladder **190**, centralization of the distal portion of catheter **110** (specifically where transducers **120** are disposed) in bladder **190** may be of importance. Thus, in some embodiments, catheter **110** may be stiff, which may allow some resistance to the pull of gravity. In some other embodiments, the distal portion of catheter **110** may include a stiffening tube inserted therewithin (e.g., in a distal portion of main channel **170**) for centralizing the distal portion of catheter **110** in bladder **190** when catheter **110** is positioned therewithin.

[00107] Transducers **120** may be configured to produce ultrasonic waves. Device **100** may include at least one transducer **120**. In the exemplary embodiment of Fig. 1, device **100** includes three transducers **120**. In some embodiments, device **100** may include between 5 to 15 transducers **120**.

[00108] Transducers **120** may be configured to resonate at a frequency between 36 Kilohertz and 1 Megahertz. Optionally, transducers **120** may be configured to resonate at a frequency between 550 Kilohertz and 1 Megahertz. Alternatively, transducers **120** may be configured to resonate at a frequency between 36 Kilohertz and 550 Kilohertz. In addition, transducers **120** may be also configured to resonate at a frequency above one Megahertz. In some embodiments, transducers **120** may be configured to resonate at a frequency of 1 Megahertz. In some embodiments, transducers **120** may be configured to resonate at a frequency between 40 Kilohertz and 100 Kilohertz. In some embodiments, transducers **120** may be configured to resonate at a frequency between 40 Kilohertz and 300 Kilohertz. In some embodiments, transducers **120** may be configured to resonate at a frequency between 300 Kilohertz and 550 Kilohertz. In some embodiments, transducers **120** may be configured to resonate at a frequency between 400 Kilohertz and 550 Kilohertz. In some embodiments, transducers **120** may be configured to resonate at a frequency between 40 Kilohertz and 150 Kilohertz. In some embodiments, transducers **120** may be configured to resonate at a frequency between 50 Kilohertz and 200 Kilohertz. In some embodiments, transducers **120**

may be configured to resonate at a frequency between 150 Kilohertz and 200 Kilohertz. In some embodiments, transducers **120** may be configured to resonate at a frequency between 170 Kilohertz and 190 Kilohertz. In some embodiments, transducers **120** may be configured to resonate at a frequency about 180 Kilohertz. In some embodiments, transducers **120** may resonate at one of the frequencies ranges listed above and may be additionally configured to resonate at a frequency above 1 Megahertz. In some embodiments, transducers **120** may be additionally configured to resonate at a frequency between 1 and 5 Megahertz. Such transducers may be used to improve the delivery of a therapeutic agent through the non-thermal cavitation mechanism, which is usually attributed to low frequencies, and the thermal mechanism, which is usually attributed to high frequencies, resulting in hyperthermia of the bladder tissue. Such hyperthermia of the bladder may have therapeutic effects solely due to the heating of the bladder wall. The synergistic thermal and cavitation effects may improve the therapeutic treatment of the bladder.

[00109] In some embodiments, in which cavitation boosters are delivered to the medium between the balloon and the bladder internal surface, transducers **120** may be configured to resonate at a frequency above one Megahertz. Such frequency level may achieve both cavitation and hyperthermia due to the addition of the cavitation boosters. Thus, a synergistic effect may be achieved by causing a synchronous cavitation of the cavitation boosters and heating of the bladder. This may improve the therapeutic treatment of the bladder. In some embodiment, usage of the cavitation boosters may be made while operating transducers **120** at a frequency below one Megahertz.

[00110] Ultrasound energy may desirably irradiate the entire internal surface of bladder **190** in order to achieve a uniform transfer of therapeutic agent **145** to bladder **190** (i.e., entirely). In order to achieve that, different configurations and shapes of transducers **120** may be utilized.

[00111] Transducers **120** may be disposed about the distal portion of catheter **110**. For example, one or more of transducers **120** may be disposed on an outer surface of the distal portion of catheter **110** or one or more of transducers **120** may be disposed within the distal portion of catheter **110**. Transducers **120** may be disposed in the distal portion of catheter

110 with gaps therebetween. Transducers **120** may be disposed within balloon **130**, as shown in Fig. 1.

[00112] Transducers **120** may be shaped in various forms, such as radial forms, e.g., a tube (i.e., tubular transducers), or flat forms, e.g., a flat rectangular or a disc. Transducers **120** of different shapes may be mounted on or disposed within catheter **110**.

[00113] In some embodiments, transducers **120** may be covered with a layer made of, e.g., silicone, polyurethane, epoxy, and parylene, in order to protect transducers **120**, attach them to catheter **110**, and/or allow their easy passage through the urethra. The layer thickness may be between 0.009 mm to 0.7 mm. In some embodiments, in which transducers **120** are mounted on a standard silicone Foley catheter, a continuous cover, made, for example, of silicone, may be applied covering the catheter and ultrasound transducers **120**. A cover made of silicone material may be used which may allow the silicone glue to adhere strongly to the silicone catheter. In addition, the silicone cover may be relatively elastic, thus allowing for an easier and safer passage of transducers **120** through the urethra. Lastly, the silicone cover may protect transducers **120** from damage which may be caused by cavitation.

[00114] Transducers **120** may be piezo elements (i.e., piezoelectric transducers). In some embodiments, transducers **120** may be structured to produce a non-focused diverging acoustic field, for example, by using tubular piezo elements. Tubular transducers may surround a section of the catheter. With reference to Fig. 1, one configuration of such tubular piezo elements is shown. Thus, transducers **120** surround a section of the distal portion of catheter **110**. Thus, transducers **120** may radiate ultrasonic waves **125** outwards in the radial direction, thereby allowing treating of at least the entire internal surface of bladder **190** synchronously. In such configuration, at least one piezo tube (i.e., transducer **120**) may be used to treat bladder **190**. In order to maintain catheter flexibility, a multiplicity of piezo tube elements which may have gaps separating between them may be used.

[00115] The length of a tubular transducer may range between 0.9 millimeter (mm) and 30 mm. In some embodiments, the length of each tubular transducer may be between 1 to 50 mm. In some embodiments, the length of each tubular transducer may be between 50 to 110 mm. In some embodiments, the length of each tubular transducer may be between 0.9 to 30

mm. In some embodiments, the length of each tubular transducer may be between 1 to 30 mm. In some embodiments, the length of each tubular transducer may be between 3 to 30 mm. In some embodiments, the length of each tubular transducer may be between 10 to 30 mm. In some embodiments, the length of each tubular transducer may be between 20 to 30 mm. In some embodiments, the length of each tubular transducer may be between 15 to 25 mm. In some embodiments, the length of each tubular transducer element may be between 80 to 100 mm. In some embodiments, the length of each tubular transducer may be about 20 mm. In some embodiments, the length of each tubular transducer may be about 30 mm.

[00116] The outer diameter of the tubular transducers may be between 2.7 to 11 mm and the inner diameter may be between 1.8 to 10 mm. In some embodiments, the outer diameter of the tubular transducers may be between 5.4 to 7.7 mm and the inner diameter may be between 3.6 to 6.6 mm. In some embodiments, the outer diameter of the tubular transducers may be between 5 to 8 mm and the inner diameter may be between 3 to 6 mm. In some embodiments, the outer diameter of the tubular transducers may be between 5 to 7 mm and the inner diameter may be between 3 to 5 mm. In some embodiments, the outer diameter of the tubular transducers may be between 6 to 8 mm and the inner diameter may be between 4 to 6 mm.

[00117] The gaps length between transducers **120** may be between 0.9 to 22 mm. Transducers **120** of different lengths and/or outer diameters may be mounted on or within catheter **110**. Furthermore, the gaps between transducers **120** may be of different lengths.

[00118] In some embodiments, transducers **120** which are flat (e.g., in the form of a flat rectangular or a disc) may be used. Such flat transducers may produce non-focused ultrasonic radiation. In such a configuration, at least one flat transducer may be mounted on or disposed within the catheter. A disc-shaped transducer may surround a section of the catheter. In using flat transducers, one may avoid energy drop over distance which may be caused when using tubular (i.e., radial) transducers, thereby allowing bladder wall treatment at higher intensities. However, flat transducers may not provide the multidirectional coverage provided by the tubular or radial ones. Thus, in some embodiments, several flat transducers may be mounted on or disposed within the catheter, while each transducer may be positioned to irradiate a different section of the bladder wall. In one optional

configuration, the flat transducers may be arranged around a section of the catheter to form various three-dimensional shapes such as a three-dimensional triangle or a cube. Such forms may be achieved by using, for example, three or four flat rectangular transducers correspondingly.

[00119] In some embodiments, the length of a flat transducer may be between 2.7 to 16.5 mm. In some embodiments, the length of a flat transducer may be between 6 to 13.5 mm. In some embodiments, the length of a flat transducer may be between 2.7 to 10.5 mm. In some embodiments, the length of a flat transducer may be between 9 to 16.5 mm. In some embodiments, the length of a flat transducer may be between 2.7 to 6 mm. In some embodiments, the length of a flat transducer may be between 13 to 16.5 mm.

[00120] In some embodiments, the width of a flat transducer may be between 1.8 to 11 mm. In some embodiments, the width of a flat transducer may be between 1.8 to 6.5 mm. In some embodiments, the width of a flat transducer may be between 6.5 to 11 mm. In some embodiments, the width of a flat transducer may be between 4 to 9 mm. In some embodiments, the width of a flat transducer may be between 1.8 to 5 mm. In some embodiments, the width of a flat transducer may be between 8 to 11 mm.

[00121] In some embodiments, the thickness of the flat transducer may be between 2 microns to 4 mm. In some embodiments, the thickness of the flat transducer may be between 0.2 mm to 4 mm. In some embodiments, the thickness of the flat transducer may be between 0.2 mm to 1 mm. In some embodiments, the thickness of the flat transducer may be between 1 mm to 4 mm. In some embodiments, the thickness of the flat transducer may be between 1 mm to 2 mm. In some embodiments, the thickness of the flat transducer may be between 200 microns to 500 microns. In some embodiments, the thickness of the flat transducer may be between 3.5 mm to 4 mm.

[00122] In some embodiments, transducers **120** may be intermittently operated at a relatively low and a relatively high frequency, such that the relatively low frequency creates cavitation and the relatively high frequency heats bladder **190**. This may be achieved by operating transducers **120** in their relatively low harmonic and their relatively high harmonic, respectively. Alternatively, this may be achieved by different ones of transducers **120** having a different resonant frequency at their first harmonic.

[00123] Reference is now made to Figs. 2A and 2B. Fig. 2A shows a side view and partially exploded of a distal portion of an exemplary urinary catheter **200**, which incorporates a flat rectangular ultrasonic transducer **210** (or simply 'transducer **210**'), according to another embodiment. Fig. 2B shows a top view of flat rectangular ultrasonic transducer **200** of Fig. 2A. Transducer **210** is formed as a flat rectangular. Transducer **210** may be integrated with catheter **200** by removing an outer section of the distal portion of catheter **200** and replacing it with transducer **210**. Such integration of catheter **200** and transducer **210** may allow easier insertion of the device through the urethra.

[00124] Since the transducers of a device according to embodiments, may be in a distance of a few centimeters from the bladder internal surface, high electric power may be delivered to the transducers in order to receive a high acoustic output close to the inner surface of the bladder wall. Thus, in some embodiments, the transducers may be wired in a separate manner (i.e., each separately coupled with the power source), in order to allow exciting each of the transducers separately. A separate excitation of the transducers may allow using lower electric energy.

[00125] Referring now to Fig. 1, balloon **130** may enclose transducers **120**, inter alia, in order to distance transducers **120** from any cavitation effects that may be formed as a result of their operation. In some embodiments, transducers **120** may be internally enclosed by balloon **130** by disposing transducers **120** inside balloon **130**. Optionally, transducers **120** may be disposed upon a portion of catheter **110** which is enclosed by balloon **130**.

[00126] In some embodiments, balloon **130** may have a maximal diameter which is above 0 and up to 11 cm. In some embodiments, balloon **130** may have a diameter which is above 0 and up to 5.5 cm. In some embodiments, balloon **130** may have a maximal diameter which is between 5.5 and 11 cm. In some embodiments, balloon **130** may have a maximal diameter which is between 2.5 and 8 cm. In some embodiments, balloon **130** may have a maximal diameter which is above 0 and up to 3 cm. In some embodiments, balloon **130** may have a maximal diameter which is between 8 and 11 cm.

[00127] In some embodiments, balloon **130** may have a length which is between 1 cm and 10 cm. In some embodiments, balloon **130** may have a length which is between 3 cm and 7.5 cm. In some embodiments, balloon **130** may have a length which is between 1 cm and

4 cm. In some embodiments, balloon **130** may have a length which is between 7 cm and 10 cm. In some embodiments, balloon **130** may have a length which is between 1 cm and 5.5 cm. In some embodiments, balloon **130** may have a length which is between 5.5 cm and 10 cm.

[00128] Balloon **130** may secure the distal portion of catheter **110** in bladder **190**, once inserted within, similarly to a standard Foley catheter balloon. In some embodiments, device **100** may include an additional balloon (i.e., in addition to balloon **130**), configured to secure the distal portion of catheter **110** in bladder **190**.

[00129] Balloon **130** may incorporate (i.e., when transducers **120** are disposed inside balloon **130**) and/or cover transducers **120**. Hence, in deflated state, during insertion through a urethra, balloon **130** may protect the urethra passage and may allow for a more smooth and easy insertion of device **100**.

[00130] As described above, in order to increase therapeutic delivery to the bladder tissue, ultrasound cavitation bubbles should form in the fluid near the bladder internal surface. Thus, balloon **130** may be configured to be filled with an acoustic coupling medium (not shown), in which, cavitation bubbles are less likely to form. This may ensure that bubble formation will not occur adjacent to transducers **120**, thereby ultrasound energy directed to an internal surface of bladder **190** may not be blocked. On the other hand, the space between balloon **130** and bladder **190** may be filled with the therapeutic fluid which may include therapeutic agent **145**. In the therapeutic fluid, cavitation bubbles **185** may be formed, as it contains dissolved gas. The difference in cavitation threshold between the acoustic coupling medium in the balloon and the fluid that fills the space between the balloon and the bladder may distance the cavitation phenomenon from the transducer. This may allow bringing cavitation effects closer to the internal surface of bladder **190** and facilitate ultrasound delivery of therapeutic agent **145**.

[00131] In some embodiments, the therapeutic fluid may include cavitation booster, which may encourage cavitation, for example, contrast agents, such as microbubbles, micro-particles, nano-particles, liposomes, or gas, such as high concentration of gases (e.g., oxygen and argon). This may increase the likelihood of forming cavitation in the space between balloon **130** and the internal surface of bladder **190**, thereby improving the transfer

of therapeutic agent **145** into bladder **190**. In case microbubbles are used, transducers **120** may be activated at a frequency between 0.7 to 10 Megahertz. In some embodiments, transducers **120** may be activated at a frequency between 0.9 to 2.5 Megahertz.

[00132] In some embodiments, in which transducers **120** are disposed inside balloon **130**, one may use a cold acoustic coupling medium (e.g., of a temperature between 5 to 20 Celsius degrees) for the purpose of cooling transducers **120**. When delivering high electric power to transducers **120**, which may result in a high heat build-up, bladder **190** and/or transducers **120** may be at risk of being damaged (e.g., by causing hyperthermia). Thus, cooling of transducers **120** may be required. In some embodiments, the cold acoustic coupling medium may, in addition, be circulated within balloon **130** via inlet channel **160** and outlet channel **165**. In some embodiments, device **100** may incorporate a temperature sensor configured to monitor the temperature of transducers **120** and ensure that the temperature of transducers **120** does not exceed a predefined threshold temperature. The threshold of the temperature may be, for example, between 90° and 250° Celsius.

[00133] The thickness of standard balloons used in prior art intravesical treatments may range between $2 \cdot 10^{-2}$ and $10 \cdot 10^{-2}$ mm. Since the disclosed ultrasonic therapeutic agent delivery utilizes cavitation effects, and in some cases, significant cavitation effects, a thicker balloon may be required in order to prevent damage or holes in the balloon. Thus, in some embodiments, the thickness of balloon **130** may be between $2 \cdot 10^{-2}$ mm and $2 \cdot 10^{-1}$ mm. In some embodiments, the thickness of balloon **130** may be between $2 \cdot 10^{-2}$ and $10 \cdot 10^{-2}$ mm. In some embodiments, the thickness of balloon **130** may be above $10 \cdot 10^{-2}$ and up to $2 \cdot 10^{-1}$ mm. In some embodiments, the thickness of balloon **130** may be above $10 \cdot 10^{-2}$ and up to $1.5 \cdot 10^{-1}$ mm. In some embodiments, the thickness of balloon **130** may be between $1.5 \cdot 10^{-1}$ and $2 \cdot 10^{-1}$ mm. In some embodiments, the thickness of balloon **130** may be between $1.8 \cdot 10^{-1}$ and $2 \cdot 10^{-1}$ mm.

[00134] The power source of console **195** may supply power to the transducers **120** via electrical wires **180**. The pump of console **195** may pump the acoustic coupling medium out of balloon **130**. In some embodiments, the pump may be used to circulate the acoustic coupling medium, e.g., via inlet channel **160** and outlet channel **165**, in order to cool transducers **120**.

[00135] A device according to some of the disclosed embodiments may further include a rotating unit configured to rotate the one or more ultrasonic transducers mounted on or disposed within the ultrasonic catheter when the device is placed within the urinary bladder. Such rotating unit may be required, for example, when using a single or few ultrasonic transducers which may not ultrasonically irradiate a sufficient portion or a desired portion of the bladder.

[00136] When device **100** is introduced into bladder **190**, balloon **130** may be filled with the acoustic coupling medium and transducers **120** may be activated to direct ultrasound waves **125** towards the internal surface of bladder **190**. Cavitation bubbles **185** may be formed in the delivered therapeutic fluid, which may include therapeutic agent **145**, adjacent to the internal surface of bladder **190**. Little or no cavitation bubbles may be formed in proximity to transducers **120**. Thereby, increasing the permeability of bladder **190** and facilitating the delivery of therapeutic agent **145** to bladder **190**.

[00137] The distance between the balloon and the bladder internal surface may be of importance. This is since cavitation bubbles **185** may form in the fluid there between. A distance between the balloon and the internal surface of the bladder which is too large, may decrease the likelihood of cavitation bubbles forming adjacent to the bladder internal surface and thus interacting with it. A smaller distance between the balloon and the bladder internal surface may increase the chances that cavitation bubbles will form adjacent to the bladder, and increase delivery of therapeutic agents to the bladder. On the other hand, if the balloon touches the bladder internal surface, this may prevent cavitation bubbles generation at the contact areas since at such areas there may be no fluid in which cavitation may form. A small distance between the balloon and the bladder (e.g., a thin layer of fluid between the balloon and the bladder) will maximize the formation of cavitation bubbles that interact with the bladder wall.

[00138] In some embodiments, a balloon may be designed such that its inflated configuration allows varying distances from the bladder internal surface, in specific areas. This design may be utilized in order to achieve varying degrees of cavitation and/or eliminate cavitation of these specific areas.

[00139] In some embodiments, the diameter of the inflated balloon **130** may vary along a longitudinal axis of balloon **130**. More specifically, in some embodiments, balloon **130** may have certain sections that may inflate to different sizes (i.e., having different diameters). For example, balloon **130** may have a distal portion which may inflate to a diameter which is larger than the diameter of its middle portion, and its middle portion may inflate to a diameter which is larger than its proximal portion diameter. In such a configuration, the shape of balloon **130** may be shaped similarly to the shape of the bladder, but smaller in size, advantageously, as small as possible without the balloon touching the bladder internal surface. Other optional shapes may be a sphere, an elongated cylinder, an elongated cylinder having two lateral sides which are larger in diameter than a middle portion, an inverted pyramid, a conical shaped balloon or the like. In some embodiments the balloon may have an asymmetric shape. In some embodiments, the balloon may not touch the internal surface of the bladder. In some embodiments, the balloon may touch the internal surface of the bladder. In some embodiment the balloon shape may be designed such that it touches the bladder wall at a certain area such that it eliminates drug delivery to this area in the bladder. For example, a balloon which has a shape of an elongated cylinder having two lateral sides which are larger in diameter than its middle portion may touch the bladder internal surface by its two lateral portions, and the therapeutic fluid may flow or reside there between, in a space formed between the middle portion of the balloon and the bladder internal surface. For yet another example, in order to deliver Botox to the bladder and avoid its delivery to the trigone of the bladder, the balloon may be designed to touch the trigone (elongated cylinder designed to thereby eliminating drug delivery to the trigone).

[00140] In some embodiments, multiple balloons **130** of various shapes may be used. In such embodiments, each of multiple balloons **130** may enclose one or more of transducers **120**.

[00141] Reference is now made to Fig. **3**, which shows a device **300**, in accordance with another embodiment. Device **300** is substantially similar to device **100** of Fig. 1 but further includes spacers **332**. Optionally, balloon **330**, corresponding to balloon **130** of Fig. 1, is equipped with spacers **332** (e.g., bulges) which are configured to distance balloon **330** from a bladder wall (not shown) allowing therapeutic fluid to reside between balloon **330** and the bladder wall. Optionally, a height of at least some of spacers **332** may range between 0.01-

20 millimeters (mm). Optionally, spacers **332** may be of equal heights. Alternatively, spacers **332** may differ in heights. Optionally, spacers **332** may be disposed upon and inflated with balloon **330**. Alternatively, spacers **332** may be part of balloon **330**, namely – portions of the balloon which, when the balloon is inflated, inflate to form bulges. Optionally, in order to prevent the bladder wall from collapsing in between the spacers **332**, a distance between each spacer (e.g., bulge) and its closest neighboring spacer should not exceed 1 centimeter. Optionally, the distance between neighboring spacers **332** is less than 1.5, 1, or 0.5 centimeters. Alternatively the spacers may be made of ridges that encircle the balloon but are but an integral part of it.

[00142] Reference is now made to Fig. **4**, which shows a top view and partially transparent of an exemplary device **400** disposed within a urinary bladder **490**, in accordance with another embodiment. Device **400** is substantially similar to device **100** of Fig. **1** with the notable difference that device **400** further includes a structure **434** placed around balloon **430**, corresponding to balloon **130** of Fig. **1**. Optionally, structure **434** may expand upon expansion of balloon **430**. Structure **434** may trap cavitation nuclei (seeds) and increase cavitation phenomenon in the therapeutic fluid. Structure **434** may be in a form of a net or a mesh of wires **436**. Examples of suitable materials include: plastic, nitinol, stainless steel, nylon, HDPE, polyethylene, cobalt based alloys, PEEK and the like. Optionally, structure **434** may entrap air bubbles, so when the user starts the treatment these air bubbles may serve as cavitation nuclei and thus may reduce significantly the cavitation threshold and increase cavitation intensity. Optionally, structure **434** may serve to distance balloon **430** from a bladder wall **490**. This may facilitate reducing a distance between the balloon **430** and a bladder wall **498** to a minimal value limited by a thickness of wires **436**. In this case the cavitation may take place only in the vicinity of the bladder wall and its efficiency will be maximal. Since the usage of the net may reduce the cavitation threshold, this may allow lower acoustic output thus reducing the risk of adverse effects. In some embodiments, the thickness of wires **436** may be between 0.1 mm to 1 mm, 0.1 mm to 0.8 mm, 0.1 mm to 0.7 mm, 0.1 mm to 0.6 mm, 0.1 mm to 0.5 mm, 0.2 mm to 0.6 mm, 0.3 mm to 0.8 mm, 0.3 mm to 0.6 mm, or 0.4 mm to 0.6 mm. Each possibility represents a separate embodiment of the present invention. In some embodiments, the thickness of the wires may vary between different areas of the net.

[00143] Optionally, openings **438** in the net or mesh are big enough to allow passage of fluid through such openings. Optionally, openings **438** are small enough to prevent the bladder wall from collapsing into the openings **438**. In some embodiments, a diameter of openings **438** may be between 50 micrometers to 2 millimeters, 50 micrometers to 1.5 millimeters, 50 micrometers to 1 millimeter, 100 micrometers to 2 millimeters, 100 micrometers to 1.5 millimeters, or 100 micrometers to 1 millimeter. Each possibility represents a separate embodiment of the present invention. Optionally diameters of openings **438** may vary between different portions/areas of the net or mesh. For a non-limiting example, specific areas of the net or mesh may include openings **438** in the net or mesh that allow portions of the bladder wall to collapse into the openings and contact the surface of the balloon, thereby preventing cavitation bubbles from forming in these portions of the bladder wall.

[00144] Reference is now made to Fig. **5**, which shows a device **500**, in accordance with another embodiment. Device **500** is substantially similar to device **400** of Fig. **4** with the notable difference that device **500** further includes spacers **532** corresponding to spacers **332** of Fig **3**.

[00145] Reference is now made to Fig. **5B**, which shows a top view and partially transparent of device **500** of Fig **5A** disposed within a urinary bladder **590** in accordance with an embodiment.

[00146] Reference is now made to Figs. **6** and **7**. Fig. **6** shows a perspective view of an exemplary device **600** according to a further embodiment. Fig. **7** shows a perspective view of an exemplary device **700** according to yet another embodiment.

[00147] Device **600** may include a urinary catheter **610**, a balloon **640** and an ultrasonic transducer **630**. Device **600** may be similar to device **100** of Fig. **1** with the required modifications. Urinary catheter **610** may be similar to catheter **110** and may include a main channel **650**, an inlet channel **660**, an outlet channel **670** and electrical wires **680**. Balloon **640** may include a dent **620** on which ultrasonic transducer **630** is mounted. Ultrasonic transducer **630** of exemplary device **600** is formed as a flat rectangular.

[00148] Device **700** may include a urinary catheter **710**, a balloon **730** and a plurality of ultrasonic transducers **720**. Device **700** may be similar to device **100** of Fig. **1** with the

required modifications. Urinary catheter **710** may be similar to catheter **110** and may include a main channel **740**, an inlet channel **750**, an outlet channel **760** and electrical wires **770**. Ultrasonic transducers **720** may be relatively small in size (i.e., to allow numerous such transducers) and may be scattered on the surface of balloon **730**. For example, ultrasonic transducers **720** may be interlaced on wires which may encircle at least a portion of balloon **730**.

[00149] As shown, in devices **600** and **700**, transducers **630** and **730**, correspondingly, are mounted on balloons **640** and **720**, correspondingly. Thus balloons **640** and **720** may be used to position transducers **630** and **730**, correspondingly, closer to the bladder internal surface. In such configurations, the transducers may be activated at lower frequencies in comparison to the configurations in which the transducers are mounted on or disposed within the catheter.

[00150] Reference is now made to Fig. 8 which shows a system **800**, in accordance with another embodiment. System **800** is substantially similar to device **100** described in Fig. 1 with the notable difference that one or more ultrasonic transducers **820**, corresponding to ultrasonic transducers **120** of Fig. 1 above, are positioned externally to the urinary bladder **890**, rather than disposed within a balloon **830** corresponding to balloon **130** as shown in Fig. 1. Optionally, one or more ultrasonic transducers **820** are positioned on a skin surface **892** of a body in close proximity to bladder **890**. Similarly to transducers **120**, one or more transducers **820** may be configured to emit ultrasonic waves **825** towards the internal surface of bladder **890**.

[00151] System **800** may further include a urinary catheter **810** (or simply 'catheter **110**') corresponding to urinary catheter **810** of Fig. 1. Optionally, balloon **830** may be mounted on a distal portion of catheter **810**. System **800** may further include electrical wires **880** corresponding to electrical wires **180** of Fig. 1. System **800** may be operatively coupled with a console **895**, via electrical wires **880**. Optionally, console **895** may include a power source. Electrical wires **880** may operatively couple one or more transducers **820** with the power supply of console **895**. Optionally, console **895** may further include one or more pumps (not shown). One or more pumps of console **895** may pump an acoustic coupling medium out of balloon **830**.

[00152] After system **800** is introduced into bladder **890**, balloon **830** may be filled with the acoustic coupling medium and transducers **820** located externally to bladder **890** may be activated to direct ultrasound waves **825** towards the internal surface of bladder **590**. Optionally, therapeutic fluids which includes therapeutic agent **845** may be introduced to urinary bladder **890** via an opening **850** positioned at the distal portion of catheter **810**. Cavitation bubbles **885** may be formed in the delivered therapeutic fluid, which may include therapeutic agent **845**, adjacent to the internal surface of bladder **590**. Little or no cavitation bubbles may be formed in proximity to transducer **820**. Accordingly, system **800** may increase permeability of bladder **890** and may further facilitate delivery of therapeutic agent **845** to bladder **890**.

[00153] In another embodiment, there is provided a system (not shown) substantially similar to device **100** with the notable difference that in addition to transducers **120** of device **100** the system may further include one or more transducers **820** of system **800**.

[00154] A kit including a urinary catheter, at least one ultrasonic transducer and a balloon as disclosed herein (e.g., catheter **110**, transducers **120** and balloon **130** of device **100** of fig. 1) and a reservoir containing an acoustic coupling medium is further disclosed. The acoustic coupling medium may be used with the urinary catheter in order to inflate the balloon. The acoustic coupling medium may be a cold acoustic coupling medium as disclosed herein, for example, with respect to device **100** of Fig. 1. In some embodiments, the kit may further include a reservoir including a therapeutic fluid, which may include or may not include a therapeutic agent, as herein disclosed, for example, with respect to device **100** of Fig. 1. In some embodiments, the therapeutic fluid may include a cavitation booster, as herein disclosed, for example, with respect to device **100** of Fig. 1.

[00155] Reference is now made to Fig. **9** which shows a system **900**, in accordance with another embodiment. System **900** is substantially similar to system **800** described in Fig. **8** with the notable difference that a cavitation monitor **991** is provided to communicate with ultrasonic transducers **920**, corresponding to ultrasonic transducers **820** of Fig. 5 above.

[00156] Optionally, cavitation monitor **991**, may include a detector transducer **993** (e.g., passive cavitation detector (PCD), hydrophone, to name a few) mounted on a distal portion of catheter **910**, corresponding to catheter **810** of Fig. **8** above. Optionally, detector

transducer **993** may be disposed within a balloon **930** corresponding to balloon **830** of Fig. 5 above.

[00157] Optionally, detector transducer **993** may include a tubular piezoelement (not shown) installed at the distal portion of catheter **610**. Due to the axial symmetry of the piezoelement the detector transducer **993** may receive acoustic signals from all directions along its length. It has 360° wide pattern directivity in the plane perpendicular to its axis, but its sensitivity is low in the axial direction. Alternatively or additionally, to achieve improved directivity in the axial direction, detector transducer **993** may include two flat piezoelements which possess pattern directivity having the maximum along the axial direction. Alternatively, detector transducer **993** may comprise a number of flat piezoelements arranged along the axial direction of catheter **910**. The maximum of the pattern directivity of each piezoelement lies in the plane perpendicular to the surface of the piezoelement and respective intersection lies along its longitudinal direction. Each element may be connected to one of the inputs of a multiplexer (not shown). Its output is connected to the input of the preamplifier. The multiplexer is also connected to the computer system, which controls its work. So by switching between elements we can analyze if the cavitation is distributed homogeneously over the volume/interface of the bladder or there are areas where the cavitation is absent.

[00158] Detector transducer **993** may acquire acoustic emissions signals applied by ultrasonic transducers **920**. Optionally, the signals received by detector transducer **993** may be amplified using a pre-amplifier **994** and may be further converted to digital signals by an analog to digital converter (ADC) **996**.

[00159] Optionally, control unit **997** utilizes a computer program product comprising a non-transitory computer-readable storage medium having program code embodied thereon, the program code executable by at least one hardware processor to: receive a digital signal from analog to digital converter **996**; compute a control signal from the digital signal; apply the control signal to control any of system **900** components. For a non-limiting example, the control signal may control cavitation formation by controlling power supply of console **995**, corresponding to console **895** of Fig.5. By these means, the control signal controls

acoustic energy produced by ultrasonic transducers **920**, which depends on electrical energy supplied to ultrasonic transducers **920**.

[00160] Optionally, the control signal may be computed by comparing received digital signals to reference values, wherein each reference value represents a specific degree of cavitation activity. A level of the digital signal received by control unit **997** may depend on specific types of detector transducers **993** and preamplifier **994** used for a specific system **900**. Optionally, reference values may be determined experimentally prior to treatment for each treatment setup and stored in the computer system memory (e.g., as a look up table). For a non-limiting example, when a digital signal received is found equal or slightly higher than the reference value, a control signal to maintain the electric power supplied to ultrasonic transducers **920** at a constant level is computed, thus maintaining a level of cavitation. For a non-limiting example, when the digital signal received is found to vary from the reference value, the computer computes a control signal to vary the electric power supplied to ultrasonic transducers **920** in order to increase/ decrease cavitation level to reach the reference level.

[00161] Optionally, a control unit **997** may receive the digital signals and transmit the resulting controlling signal to the corresponding component using any standard wired and/or wireless communication protocol, such as USB, Bluetooth, or WiFi. Optionally, control unit **997** may further measure other parameters such as time of operation of system **900**.

[00162] Optionally, a user-interface (not shown) may be provided allowing a user to define parameters. For example, the user may predefine a maximal time of operation for the system.

[00163] Optionally, control unit **997** may further control a duration of operation of system **600**. Optionally, control signal to stop the operation of system **900** by stopping the electric power supplied to ultrasonic transducers **920** may be computed according to predetermined one or more parameters, such as total operation time of system **900**, treatment time at a specific cavitation level, to name a few. Optionally, a control signal to stop the operation of system **900** may be computed at a specific value of an integral of V^2 , which may be reached either at low intensity cavitation and longer treatment time or at high intensity cavitation

and shorter treatment time. Optionally, specific parameters may be determined in accordance to a specific patient bladder parameters.

[00164] Typically, acoustic emission produced by the cavitation event is characterized by a wide spectrum as is schematically shown in Fig. **10A**. At the beginning, when acoustic pressure in the liquid is less than cavitation threshold there is no cavitation and noise level at an output of a pre-amplifier connected to a PCD is minimal. Acoustic pressure is increased until a sharp increase of the noise level is detected (at T_0) as is schematically illustrated in Fig. **10B**, this indicates inertial cavitation initiation. Further increase of the acoustic pressure leads to increase of cavitation noise level. Cavitation bubbles strongly attenuate and scatter the high intensity acoustic signal emitted by an ultrasound transducer. The shock waves produced by collapsing bubbles are also scattered and attenuated by the bubbles within the cavitation cloud, therefore increase of cavitation noise level is not linearly proportional to the increase of acoustic energy emitted by the transducer. Alternative estimation of the intensity of cavitation may be achieved by measuring of root-square-mean voltage V_{RMS} produced by the PCD, or the integral of the square of the voltage (V^2) as a function of time, produced by the PCD. The integral is proportional (though non-linearly) to the total acoustic energy produced by imploding bubbles and can also characterize the cavitation intensity. Fig. **10C** is a schematic representation of integration results for the cases of strong and weak cavitation, respectively.

[00165] For yet another non-limiting example, during the operation of system **900**, urinary bladder **990** is initially filled with therapeutic fluid **945**, corresponding to therapeutic fluid **845** of Fig. **8**, via an opening **950**, corresponding to opening **850** of Fig. **8**, positioned at the distal portion of catheter **910**. Control unit may be configured to monitor the noise level during treatment and gradually increase electric power provided to ultrasonic transducers **920** if said noise level values are less than a specified reference value related to cavitation initiation. Optionally, when sub-harmonics, high harmonics and ultraharmonics frequencies are detected, control unit **997** computes a control signal to maintain the acoustic energy at constant level and continue treatment for a certain time duration. Alternatively, control unit **997** computes a control signal to continue to increase the acoustic energy until levels of the subharmonic or high harmonics, or their ratio, achieve predefined values. When a predefined value is achieved control unit **997** computes a control signal to maintain the

acoustic pressure at the constant level and continue treatment for a predefined time duration. Alternatively, control unit **997** computes a control signal to continue increasing the acoustic energy until it will detect the appearance of the wideband noise which is the indication of inertial cavitation initiation.

[00166] Referring to the drawings, Fig. **11A** shows a system **1100** disposed within urinary bladder **1190**, in accordance with an embodiment. System **1100** is substantially similar to system **900** with the notable difference that a balloon **1130** corresponding to balloon **930** of Fig. **9** is filled with gas rather than acoustic coupling medium. A detector transducer **1193**, corresponding to detector transducer **993** of Fig. **9**, is positioned externally to urinary bladder **1190**, rather than disposed within balloon **1130**. Optionally, detector transducer **1193** may be a separate ultrasound transducer, or a part of an ultrasound transducer **1120**, corresponding to ultrasound transducers **920** of Fig. **9**, which applies the cavitation. Reference is now made to Fig. **11B** which shows a schematic view of an emitting surface of an ultrasound transducer **1120** (e.g., HIUT) which comprises a detector transducer **1193** (e.g., PCD)

[00167] Reference is now made to Fig. **12** which shows a system **1200** disposed within urinary bladder **1290**, in accordance with an embodiment. System **1200** is substantially similar to system **900** of Fig. **9**, with the notable difference that an ultrasound transducer **1220**, corresponding to ultrasound transducer **920** of Fig. **9**, and a detector transducer **1293**, corresponding to detector transducer **993** of Fig. **9** are arranged differently than in system **900** of Fig. **9**. Ultrasound transducer **1220** is installed at a distal part of a catheter **1210** and a detector transducer **1293**, is placed externally on the abdomen. Optionally a balloon **1230**, corresponding to balloon **930** of Fig. **9**, is filled with degassed liquid.

[00168] Reference is now made to Fig. **13** which shows a system **1300** disposed within urinary bladder **1390**. System **1300** is substantially similar to system **900** of Fig. **9**, with the notable difference that **1320**, corresponding to ultrasound transducer **920** of Fig. **9**, and a detector transducer **1393**, corresponding to detector transducer **993** of Fig. **9**, are placed on a distal part of a catheter of a catheter **1210**, corresponding to catheter **910** of Fig. **9**. Optionally a balloon **1330**, corresponding to balloon **930** of Fig. **9**, is filled with degassed liquid.

[00169] Reference is now made to Figs. **12** and **13A-13C**. Fig. **12** shows a flowchart of a method for delivering a therapeutic fluid to the urinary bladder, constructed and operative in accordance with an embodiment of the disclosed technique. Fig. **13A** shows the device of Fig. **1** when inserted into the urinary bladder, according to the method of Fig. **12**. Fig. **13B** shows the device of Fig. **1** when inflated inside the urinary bladder and therapeutic fluid is delivered to the urinary bladder, according to the method of Fig. **12**. Fig. **13C** shows the device of Fig. **1** when ultrasonic waves are applied to the urinary bladder and cavitation of the therapeutic fluid is formed, according to the method of Fig. **12**.

[00170] In a step **1400**, a distal portion of a urinary catheter and at least one ultrasonic transducer disposed thereabout is inserted into the urinary bladder. The at least one ultrasonic transducer may be enclosed by a balloon. The urinary catheter, the transducer and the balloon may be according to the urinary catheters, the transducers and the balloons disclosed herein such as catheter **110**, transducers **120** and balloon **130** of device **100** of Fig. **1**. With Reference to Fig. **15A**, a device **1500** which includes a urinary catheter **1505** (or simply 'catheter **1505**'), ultrasonic transducers **1510** (or simply 'transducers **1510**') enclosed by a balloon **1520** is inserted into a urinary bladder **1590** (or simply 'bladder **1590**'). A distal portion of device **1500** and catheter **1305** is placed in bladder **1590** and such that transducers **1510** and balloon **1520** are positioned in bladder **1590**. Balloon **1520** is entirely or mostly deflated at this stage.

[00171] In a step **1410**, the balloon may be inflated with an acoustic coupling medium via a first opening and a first longitudinal lumen of the urinary catheter. The first opening is disposed in the first longitudinal lumen and inside said balloon. The acoustic coupling medium may be a cold acoustic coupling medium. Alternatively, the acoustic coupling medium may be cooled in a further optional step. With reference to Fig. **15A**, the acoustic coupling medium may be inserted into balloon **1520** via a first longitudinal lumen of catheter **1505** (not shown) and a first opening in the first longitudinal lumen (not shown). The first opening may be disposed inside balloon **1520**. In a further optional step, the acoustic coupling medium may be continuously or intermittently circulated via an inlet channel **1550** and an outlet channel **1560**. One of inlet channel **1550** and outlet channel **1560** may be the first longitudinal lumen and may include the first opening while the other may

be a third longitudinal lumen (not shown) and may include a third opening (not shown) of catheter **1505** disposed in the third longitudinal lumen and inside balloon **1520**.

[00172] In a step **1420**, therapeutic fluid may be delivered to the urinary bladder, around the balloon and via a second longitudinal lumen and a second opening of the urinary catheter. The second opening may be disposed in the second longitudinal lumen and outside of the balloon. The therapeutic fluid may or may not include a therapeutic agent to be delivered a tissue of the urinary bladder. With Reference to Fig. **15B**, balloon **1520** is now inflated with the acoustic coupling medium within bladder **1590**. A therapeutic fluid (not shown) is inserted to bladder **1590** (i.e., to the cavity formed between balloon **1520** and internal surface **1595** of bladder **1590**). The therapeutic fluid may be inserted via a main channel **1540** of catheter **1505**, through a second longitudinal lumen **1530** of catheter **1505** and into bladder **1590** via a second opening **1535** in second longitudinal lumen **1530**. Second opening **1535** is disposed in the distal portion of catheter **1505** and outside balloon **1520**. The therapeutic fluid includes a therapeutic agent **1580** which thus may be dispersed in bladder **1590**. Optionally, the therapeutic agent is not included within the therapeutic fluid.

[00173] In an optional step, matter which encourages cavitation may be added to the therapeutic fluid. Such matter may be for example, contrast agents, such as microbubbles (e.g., Definity®, Optison® and SonoVue®) or gas, such as high concentration of gases (e.g., argon). Optionally, the gasses are inert gasses.

[00174] In a step **1430**, the at least one ultrasonic transducer may be activated to transmit ultrasonic waves towards an internal surface of the urinary bladder, to form cavitation bubbles in the therapeutic fluid adjacent to the internal surface. Little or no cavitation bubbles may be formed in the acoustic coupling medium in the balloon. By that, the permeability of the urinary bladder may be increased and the delivery of the therapeutic agent to tissue of the urinary bladder may be facilitated. The transducers may be activated continuously or intermittently. With reference to Fig. **15C**, transducers **1510** may be activated to produce ultrasonic waves **1515**. Cavitation bubbles **1585** may be formed in the therapeutic fluid, which fills the space between balloon **1520** and the bladder internal surface **1595**, thereby bringing cavitation effects closer to the bladder internal surface **1595**.

Since balloon **1520** encloses transducers **1510** and since balloon **1520** is filled with an acoustic coupling medium, little or no cavitation bubbles may be formed balloon **1520** and in adjacent to ultrasonic transducers **1510**. Optionally, the therapeutic agents may be added to the therapeutic fluid following formation of cavitation bubbles **1585**. The therapeutic agent may be added within 0.01 second to 12 hours following activation of the at least one ultrasonic transducer. Optionally, the therapeutic agent may be added, 0.1 second to 10 minutes, 1 second to 10 minutes, 1 second to 30 minutes, 1 minute to 30 minutes, 1 minute to 60 minutes, 30 minutes to 60 minutes, 1 hour to 2 hours, 1 hour to 3 hours, or 1 hour to 6 hours following activation of the at least one ultrasonic transducer. Optionally, steps 1420 and 1430 may be performed simultaneously. Alternatively step 1420 may be performed sequentially. Optionally step 1420 may follow step 1430. Alternatively, step 1430 may follow step 1420, accordingly the therapeutic agent may be added following activation of the at least one ultrasonic transducer.

[00175] The ultrasonic transducers may be activated at intensity between 0.0009 and 16.5 Watts per square centimeter in order to facilitate the delivery of the therapeutic solution. In some embodiments, the ultrasonic transducers may be activated at intensity between 0.01 and 7.5 Watts per square centimeter. In some embodiments, the ultrasonic transducers may be activated at intensity between 7.5 and 15 Watts per square centimeter. In some embodiments, the ultrasonic transducers may be activated at intensity between 5 and 10 Watts per square centimeter. In some embodiments, the ultrasonic transducers may be activated at intensity between 12 and 15 Watts per square centimeter. In some embodiments, the ultrasonic transducers may be activated at intensity between 0.01 and 4 Watts per square centimeter.

[00176] The ultrasonic transducers may be activated at a frequency between 0.018 and 11 Megahertz. In some embodiments, the ultrasonic transducers may be activated at a frequency between 0.02 and 5 Megahertz. In some embodiments, the ultrasonic transducers may be activated at a frequency between 5 and 10 Megahertz. In some embodiments, the ultrasonic transducers may be activated at a frequency between 3 and 7 Megahertz. In some embodiments, the ultrasonic transducers may be activated at a frequency between 0.02 and 3 Megahertz. In some embodiments, the ultrasonic transducers may be activated at a frequency between 8 and 10 Megahertz.

[00177] In an optional step, the catheter may be rotated in a predefined angular measure and such that different peripheral portions of the distal portion of the catheter and/or of the balloon enclosing it may face different portions of the internal surface of the bladder. The transducers may be then activated again (i.e., in case the transducers are not activated continuously). This step may be performed iteratively, for example, such that specific peripheral portion of the catheter and/or of the balloon may each time face a different portion of the internal surface of the bladder. This step may be applicable, for example, when an asymmetric balloon is used and/or when a portion of the balloon touches the internal surface of the bladder. Thus, several circles of treatment may be applied, for example, in order to treat the entire bladder. When the catheter is multiply rotated, it may be rotated each time in a fixed predefined angle or at various predefined angles.

[00178] In an optional step **1440**, therapeutic agent may be delivered to the urinary bladder. This step may be taken in cases where the therapeutic solution which was delivered to the urinary bladder according to step **1420** does not include the therapeutic agent. Since ultrasound effect of increasing tissue permeability may last for many hours following ultrasound treatment, the bladder may be first ultrasonically irradiated with ultrasound to form cavitation effects in the delivered therapeutic solution and only then washed with the therapeutic agent.

[00179] The disclosed devices and kits may be operated according to the method of Fig. **14**.

[00180] When a value is defined herein as a range between two numbers, the value may be equal to any number between these two numbers or to each of these two numbers.

[00181] Control unit **997** may include one or more software modules to perform any of the controlling, computing, receiving and/or transmitting functions described herein.

[00182] The present invention may be a system, a method, and/or a computer program product. The computer program product may include a computer readable storage medium (or media) having computer readable program instructions thereon for causing a processor to carry out aspects of the present invention.

[00183] The computer readable storage medium can be a tangible device that can retain and store instructions for use by an instruction execution device. The computer readable

storage medium may be, for example, but is not limited to, an electronic storage device, a magnetic storage device, an optical storage device, an electromagnetic storage device, a semiconductor storage device, or any suitable combination of the foregoing. A non-exhaustive list of more specific examples of the computer readable storage medium includes the following: a portable computer diskette, a hard disk, a random access memory (RAM), a read-only memory (ROM), an erasable programmable read-only memory (EPROM or Flash memory), a static random access memory (SRAM), a portable compact disc read-only memory (CD-ROM), a digital versatile disk (DVD), a memory stick, a floppy disk, a mechanically encoded device such as punch-cards or raised structures in a groove having instructions recorded thereon, and any suitable combination of the foregoing. A computer readable storage medium, as used herein, is not to be construed as being transitory signals per se, such as radio waves or other freely propagating electromagnetic waves, electromagnetic waves propagating through a waveguide or other transmission media (e.g., light pulses passing through a fiber-optic cable), or electrical signals transmitted through a wire.

[00184] Computer readable program instructions described herein can be downloaded to respective computing/processing devices from a computer readable storage medium or to an external computer or external storage device via a network, for example, the Internet, a local area network, a wide area network and/or a wireless network. The network may comprise copper transmission cables, optical transmission fibers, wireless transmission, routers, firewalls, switches, gateway computers and/or edge servers. A network adapter card or network interface in each computing/processing device receives computer readable program instructions from the network and forwards the computer readable program instructions for storage in a computer readable storage medium within the respective computing/processing device.

[00185] Computer readable program instructions for carrying out operations of the present invention may be assembler instructions, instruction-set-architecture (ISA) instructions, machine instructions, machine dependent instructions, microcode, firmware instructions, state-setting data, or either source code or object code written in any combination of one or more programming languages, including an object oriented programming language such as Smalltalk, C++ or the like, and conventional procedural programming languages, such as

the "C" programming language or similar programming languages. The computer readable program instructions may execute entirely on the user's computer, partly on the user's computer, as a stand-alone software package, partly on the user's computer and partly on a remote computer or entirely on the remote computer or server. In the latter scenario, the remote computer may be connected to the user's computer through any type of network, including a local area network (LAN) or a wide area network (WAN), or the connection may be made to an external computer (for example, through the Internet using an Internet Service Provider). In some embodiments, electronic circuitry including, for example, programmable logic circuitry, field-programmable gate arrays (FPGA), or programmable logic arrays (PLA) may execute the computer readable program instructions by utilizing state information of the computer readable program instructions to personalize the electronic circuitry, in order to perform aspects of the present invention.

[00186] Aspects of the present invention are described herein with reference to flowchart illustrations and/or block diagrams of methods, apparatus (systems), and computer program products according to embodiments of the invention. It will be understood that each block of the flowchart illustrations and/or block diagrams, and combinations of blocks in the flowchart illustrations and/or block diagrams, can be implemented by computer readable program instructions.

[00187] These computer readable program instructions may be provided to a processor of a general purpose computer, special purpose computer, or other programmable data processing apparatus to produce a machine, such that the instructions, which execute via the processor of the computer or other programmable data processing apparatus, create means for implementing the functions/acts specified in the flowchart and/or block diagram block or blocks. These computer readable program instructions may also be stored in a computer readable storage medium that can direct a computer, a programmable data processing apparatus, and/or other devices to function in a particular manner, such that the computer readable storage medium having instructions stored therein comprises an article of manufacture including instructions which implement aspects of the function/act specified in the flowchart and/or block diagram block or blocks.

[00188] The computer readable program instructions may also be loaded onto a computer, other programmable data processing apparatus, or other device to cause a series of operational steps to be performed on the computer, other programmable apparatus or other device to produce a computer implemented process, such that the instructions which execute on the computer, other programmable apparatus, or other device implement the functions/acts specified in the flowchart and/or block diagram block or blocks.

[00189] The flowchart and block diagrams in the Figures illustrate the architecture, functionality, and operation of possible implementations of systems, methods, and computer program products according to various embodiments of the present invention. In this regard, each block in the flowchart or block diagrams may represent a module, segment, or portion of instructions, which comprises one or more executable instructions for implementing the specified logical function(s). In some alternative implementations, the functions noted in the block may occur out of the order noted in the figures. For example, two blocks shown in succession may, in fact, be executed substantially concurrently, or the blocks may sometimes be executed in the reverse order, depending upon the functionality involved. It will also be noted that each block of the block diagrams and/or flowchart illustration, and combinations of blocks in the block diagrams and/or flowchart illustration, can be implemented by special purpose hardware-based systems that perform the specified functions or acts or carry out combinations of special purpose hardware and computer instructions.

[00190] The descriptions of the various embodiments of the present invention have been presented for purposes of illustration, but are not intended to be exhaustive or limited to the embodiments disclosed. Many modifications and variations will be apparent to those of ordinary skill in the art without departing from the scope and spirit of the described embodiments. The terminology used herein was chosen to best explain the principles of the embodiments, the practical application or technical improvement over technologies found in the marketplace, or to enable others of ordinary skill in the art to understand the embodiments disclosed herein.

CLAIMS

What is claimed is:

1. A kit comprising:
 - a urinary catheter comprising a first and a second longitudinal lumens;
 - at least one ultrasonic transducer disposed about a distal portion of said urinary catheter;
 - a balloon mounted on said urinary catheter at the distal portion, and enclosing said at least one ultrasonic transducer; and
 - a reservoir containing an acoustic coupling medium,wherein:
 - said urinary catheter further comprises a first opening in said first longitudinal lumen, said first opening disposed inside said balloon and configured to inflate said balloon with at least some of said acoustic coupling medium,
 - said urinary catheter further comprises a second opening in said second longitudinal lumen, said second opening disposed outside said balloon and configured to deliver a therapeutic fluid into the urinary bladder, around said balloon, and
 - activation of said at least one ultrasonic transducer in said urinary bladder causes cavitation bubbles to form in said therapeutic fluid adjacent an internal surface of the urinary bladder, and little or no cavitation bubbles are formed in said acoustic coupling medium in said balloon.
2. The kit according to claim 1, further comprising a reservoir containing said therapeutic fluid
3. The kit according to claim 1 or 2, wherein said therapeutic fluid comprises a cavitation booster selected from the group consisting of: an ultrasound contrast agent, micro-particles, nanoparticles, liposomes, and a gas.
4. The kit according to claim 1, wherein said therapeutic fluid comprises one or more therapeutic agents selected from the group consisting of: a drug, a chemotherapeutic agent, a tracer, a marker, a radioactive compound, a small molecule, and a gene.

5. The kit according to claim 4, wherein said one or more therapeutic agents are selected from the group consisting of: anti muscarinic agents, anticholinergic agents, anesthetic agents, and botulinum toxins.

6. The kit according to claim 4, wherein said chemotherapeutic agent is selected from the group consisting of: Bacillus Calmette Guerin (BCG) vaccine, cisplatin, doxorubicin, valrubicin, gemcitabine, mycobacterial cell wall-DNA complex (MCC), methotrexate, vinblastine, thiotepa, mitomycin, fluorouracil, leuprolide, diethylstilbestrol, estramustine, megestrol acetate, cyproterone, flutamide, a selective estrogen receptor modulator, botulinum toxins, and cyclophosphamide.

7. The kit according to claim 1, wherein said at least one ultrasonic transducer is structured to produce an unfocused, diverging acoustic field.

8. The kit according to claim 1, wherein said at least one ultrasonic transducer is at least one tubular transducer surrounding a section of said urinary catheter.

9. The kit according to claim 1, wherein said at least one ultrasonic transducer is a flat, rectangular transducer.

10. The kit according to claim 1, wherein said urinary catheter further comprises a third longitudinal lumen and a third opening disposed inside said balloon, to allow circulating said at least some of said acoustic coupling medium in and out of said balloon, thereby cooling said at least some of said acoustic coupling medium .

11. The kit according to claim 1, further comprising a rotation unit configured to rotate at least said at least one ultrasonic transducer when said at least one ultrasonic transducer is activated.

12. The kit according to claim 1, wherein the balloon is shaped similarly to the shape of the urinary bladder and is smaller in size than the urinary bladder.

13. The kit of claim 1, wherein said at least one ultrasonic transducer is configured to resonate at a frequency between 36 Kilohertz and 550 Kilohertz.

14. The kit of claim 1, wherein said at least one ultrasonic transducer is configured to resonate at a frequency between 36 Kilohertz and 100 Kilohertz.

15. The kit of claim 1, wherein said at least one ultrasonic transducer is configured to resonate at a frequency between 36 Kilohertz and one Megahertz and at a frequency above one Megahertz.

16. A method for delivering a therapeutic fluid to the urinary bladder, the method comprising:

inserting a distal portion of a urinary catheter and at least one ultrasonic transducer disposed thereabout into said urinary bladder, wherein said at least one ultrasonic transducer is enclosed by a balloon,

inflating said balloon with an acoustic coupling medium via a first longitudinal lumen and a first opening of said urinary catheter, wherein said first opening is disposed in said first longitudinal lumen and inside said balloon,

delivering to said urinary bladder, around said balloon, therapeutic fluid via a second longitudinal lumen and a second opening of said urinary catheter, wherein said second opening is disposed in said second longitudinal lumen and outside said balloon, and

activating said at least one ultrasonic transducer to transmit ultrasonic waves towards an internal surface of said urinary bladder, to form cavitation bubbles in said therapeutic fluid adjacent to said internal surface and little or no cavitation bubbles in said acoustic coupling medium in said balloon.

17. The method according to claim 11, wherein said therapeutic fluid comprises a cavitation booster selected from the group consisting of: an ultrasound contrast agent, micro-particles, nano-particles and a gas.

18. The method according to claim 11, wherein said at least one ultrasonic transducer is structured to produce an unfocused, diverging acoustic field.

19. The method according to claim 11, wherein said at least one ultrasonic transducer is at least one tubular transducer surrounding a section of said urinary catheter.

20. The method according to claim 11, wherein said at least one ultrasonic transducer is a plurality of flat, rectangular transducers arranged around a section of said urinary catheter.

21. The method according to claim 11, wherein said urinary catheter further comprises a third longitudinal lumen and a third opening disposed inside said balloon, and wherein said method further comprises circulating said at least some of said acoustic coupling medium in and out of said balloon via said first and third longitudinal lumens to cool said at least some of said acoustic coupling medium.

22. The method according to claim 11, further comprising rotating at least said at least one ultrasonic transducer when said at least one ultrasonic transducer is activated.

23. The method according to claim 11, further comprising rotating said urinary catheter.

24. The method according to claim 17, further comprising iteratively activating said at least one ultrasonic transducer and each time said urinary catheter is rotated.

25. A device comprising:

a urinary catheter comprising a first and a second longitudinal lumens;

at least one ultrasonic transducer disposed about a distal portion of said urinary catheter; and

a balloon mounted on said urinary catheter at the distal portion, and enclosing said at least one ultrasonic transducer;

wherein:

said urinary catheter further comprises a first opening in said first longitudinal lumen, said first opening disposed inside said balloon and configured to inflate said balloon with an acoustic coupling medium,

said urinary catheter further comprises a second opening in said second longitudinal lumen, said second opening disposed outside said balloon and configured to deliver a therapeutic fluid into the urinary bladder, around said balloon, and

activation of said at least one ultrasonic transducer in said urinary bladder causes cavitation bubbles to form in said therapeutic fluid adjacent an internal surface of the

urinary bladder, and little or no cavitation bubbles are formed in said acoustic coupling medium in said balloon.

26. The device of claim 25, further comprising a cavitation monitor, wherein said cavitation monitor acquires acoustic emissions signals and transmits a digital signal.

27. The device of claim 26, wherein said cavitation monitor comprises transducer detector disposed within said balloon.

28. The device of claim 27, wherein said transducer detector is mounted on a distal portion of said urinary catheter.

29. The device of claim 25, further comprising one or more spacers disposed on an external surface of said balloon.

30. The device of claim 25, further comprising a net surrounding said balloon.

31. The device of claim 25, wherein said balloon comprises a rough external surface.

32. A kit comprising:

at least one ultrasonic transducer;

a urinary catheter comprising a first and a second longitudinal lumens;

a balloon mounted at a distal portion of said urinary catheter; and

a reservoir containing an acoustic coupling medium,

wherein:

said urinary catheter further comprises a first opening in said first longitudinal lumen, said first opening disposed inside said balloon and configured to inflate said balloon with at least some of said acoustic coupling medium,

said urinary catheter further comprises a second opening in said second longitudinal lumen, said second opening disposed outside said balloon and configured to deliver a therapeutic fluid into the urinary bladder, around said balloon, and

activation of said at least one ultrasonic transducer causes cavitation bubbles to form in said therapeutic fluid adjacent an internal surface of the urinary bladder, and little or no cavitation bubbles are formed in said acoustic coupling medium in said balloon.

33. The kit of claim 32, wherein said ultrasonic transducer is positioned externally to said urinary bladder.

34. The kit of claim 32, wherein said ultrasonic transducer is disposed within said balloon.

35. The kit of claim 34, wherein said ultrasonic transducer is mounted on a distal portion of said urinary catheter.

36. The kit of any one of claims 32 to 35, further comprising a cavitation monitor, wherein said cavitation monitor acquires acoustic emissions signals and transmits a digital signal.

37. The kit of claim 36, wherein said cavitation monitor comprises a transducer detector disposed within said balloon.

38. The device of claim 37, wherein said transducer detector is mounted on a distal portion of said urinary catheter.

39. The kit of claim 36, wherein said cavitation monitor comprises a transducer detector disposed externally to said urinary bladder.

40. The kit of claim 36, wherein said cavitation monitor comprises a transducer detector disposed within said ultrasonic transducer.

41. The kit of claim 32, further comprising one or more spacers disposed on an external surface of said balloon.

42. The kit of claim 32, further comprising a net surrounding said balloon.

43. The kit of claim 32, wherein said balloon comprises a rough external surface.

44. The kit of claim 32, further comprising a control unit, wherein said control unit is configured to receive digital signals and to compute a control signal to control an operation of said ultrasound transducer, thereby controlling cavitation activity.

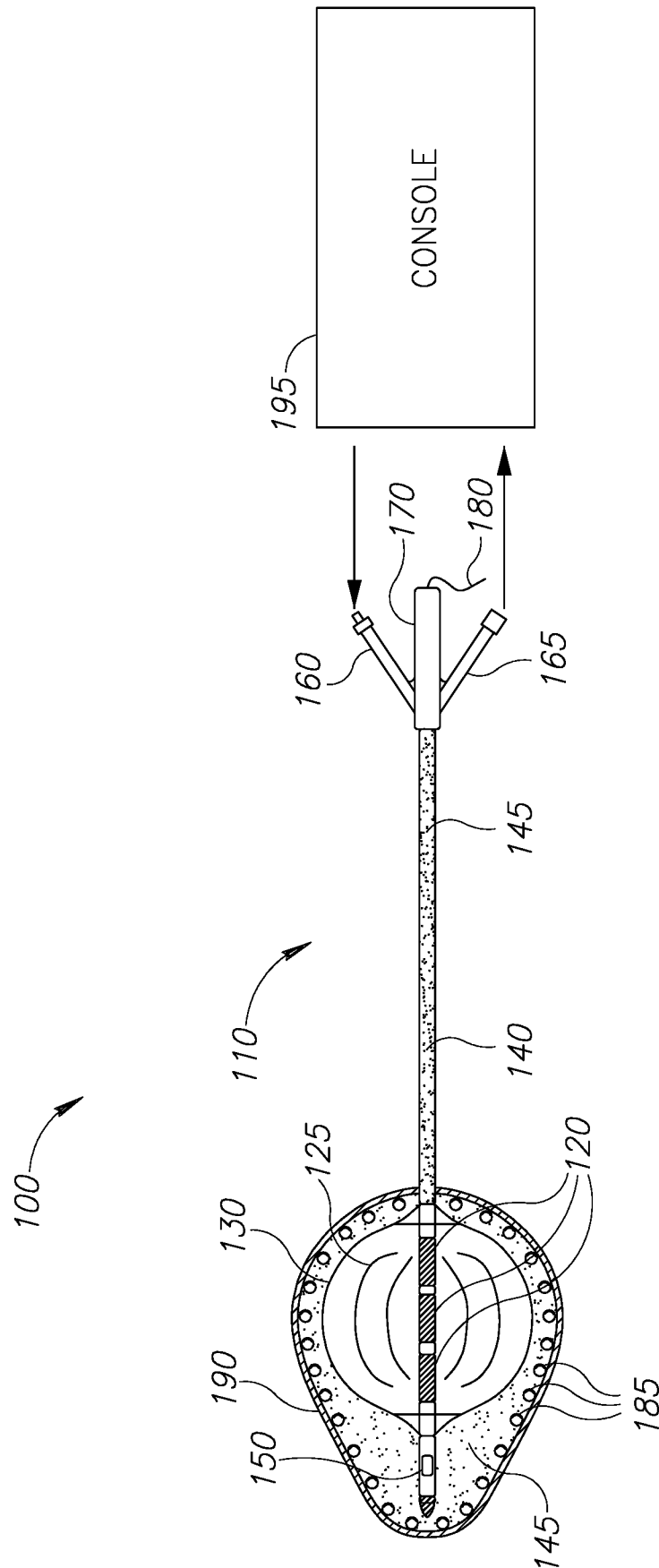


FIG.1

200

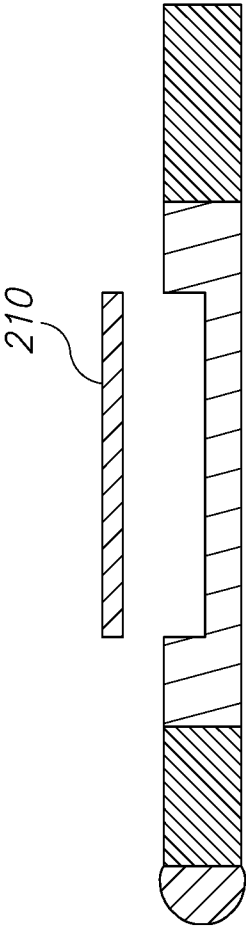


FIG. 2A

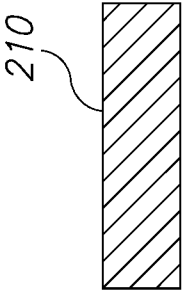


FIG. 2B

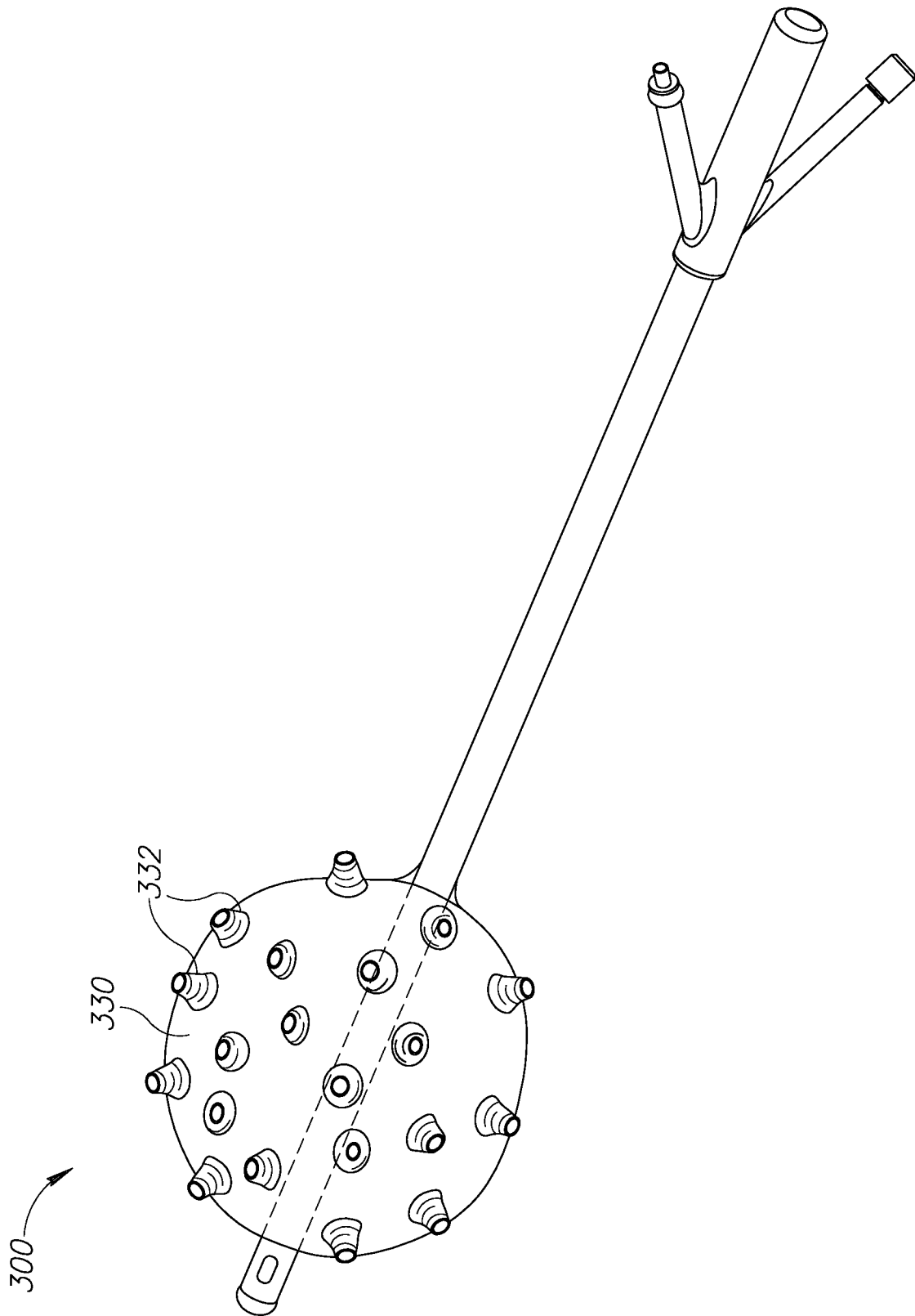


FIG. 3

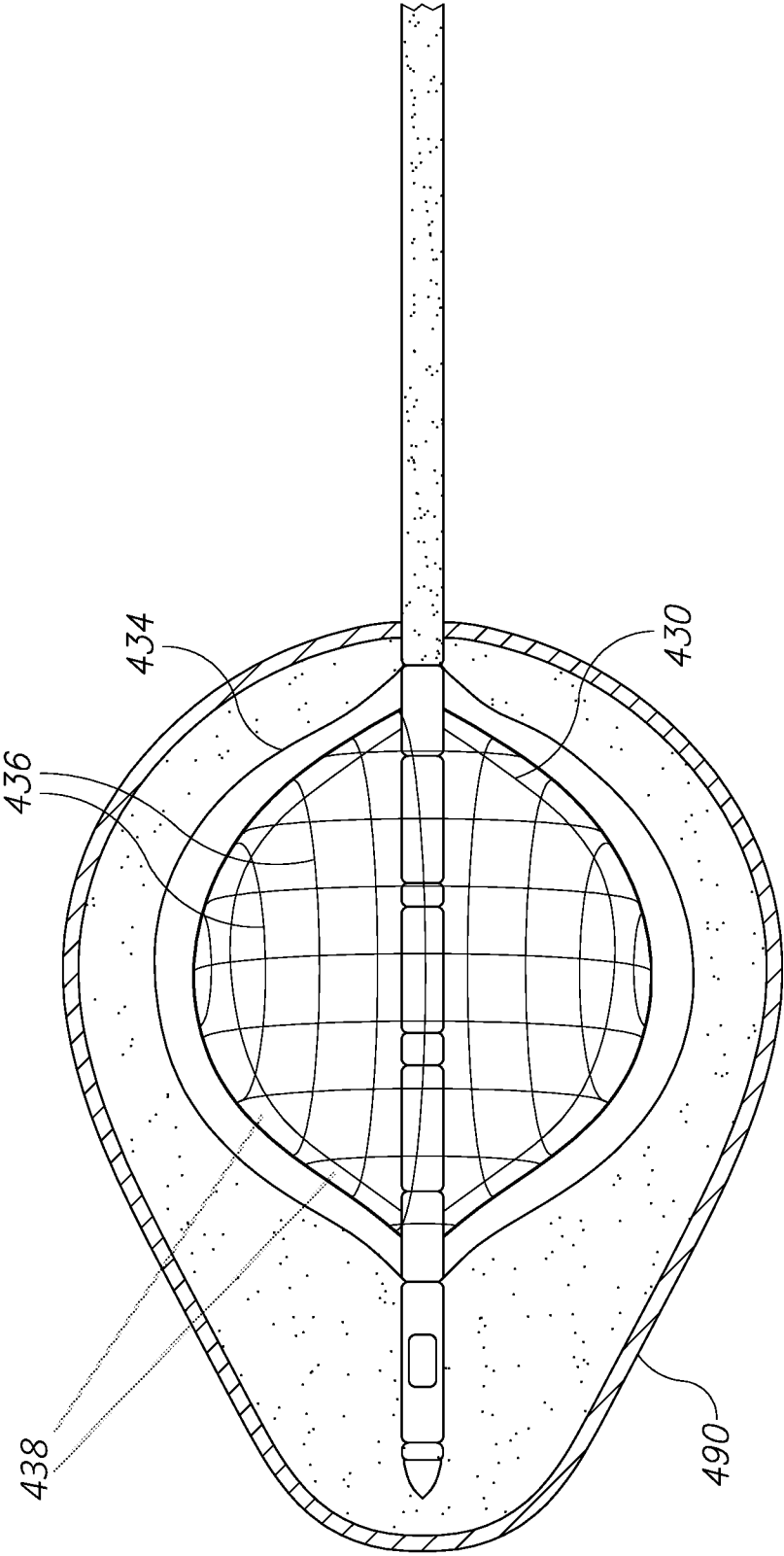


FIG. 4

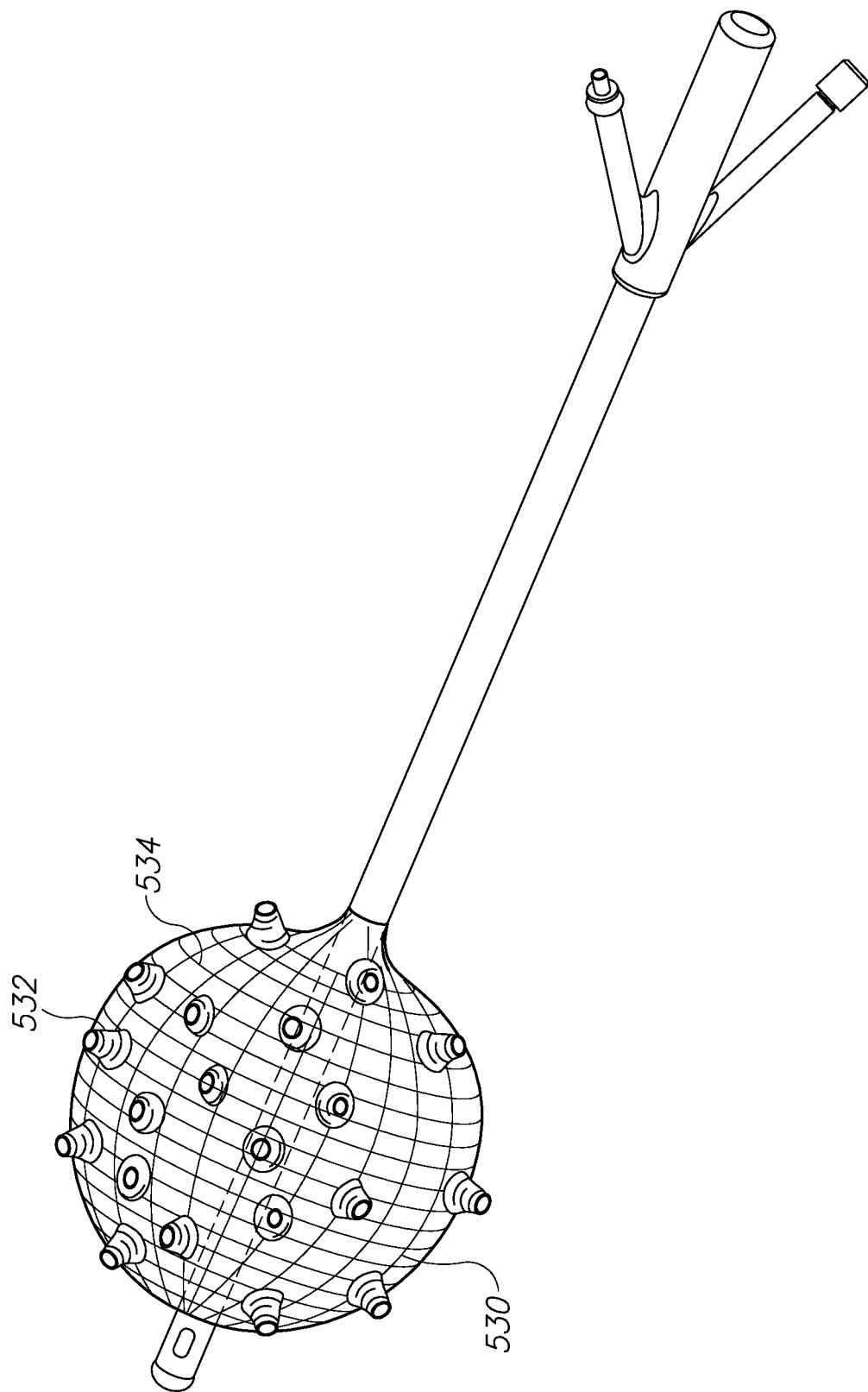


FIG. 5A

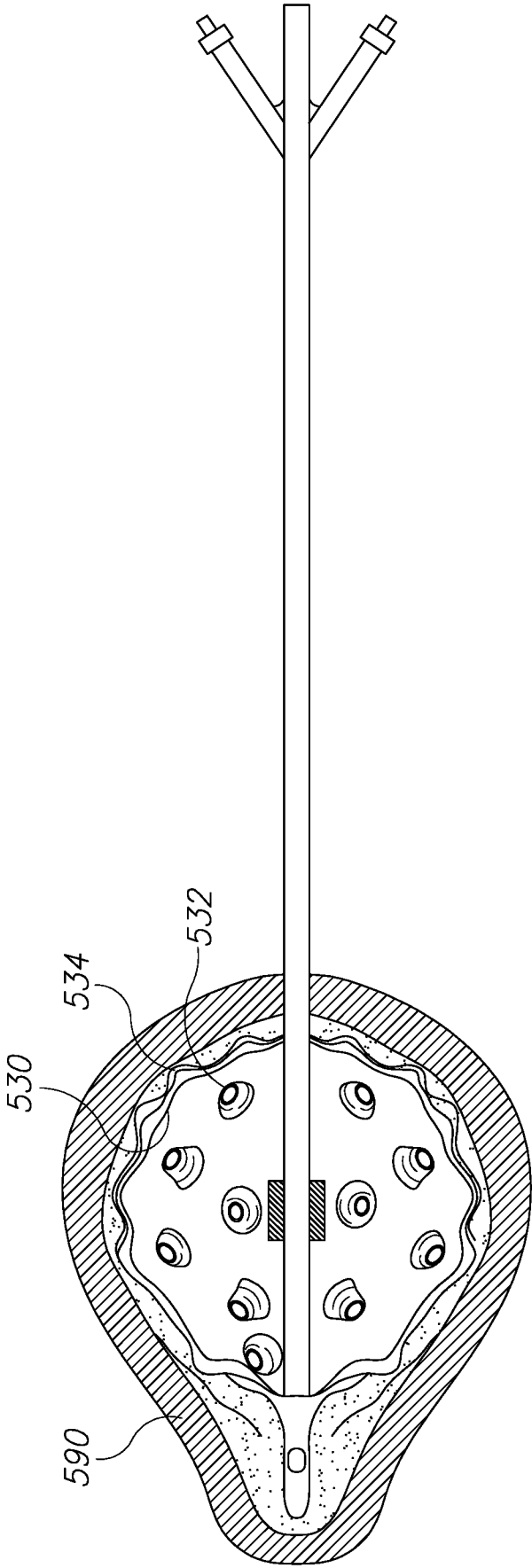


FIG. 5B

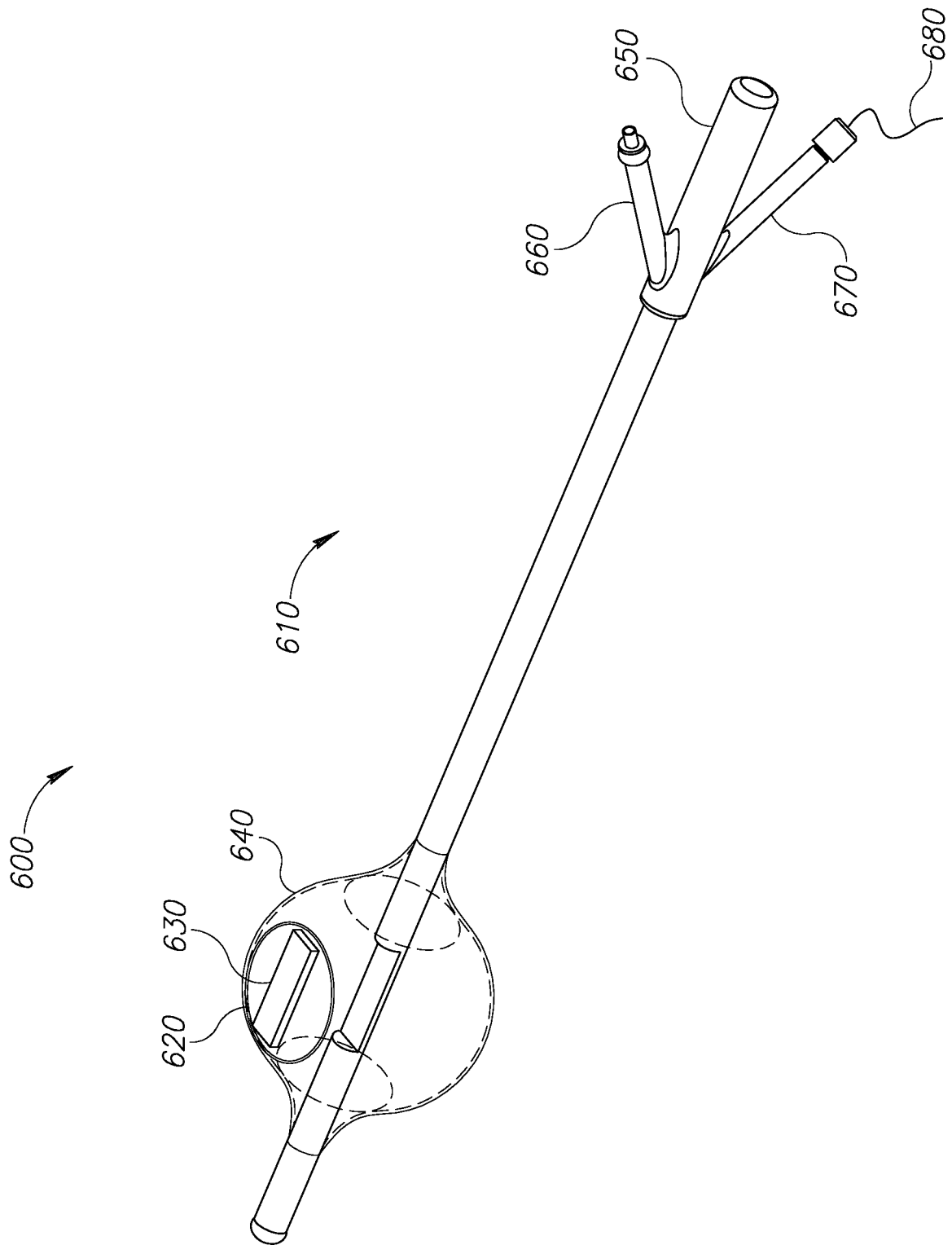


FIG. 6

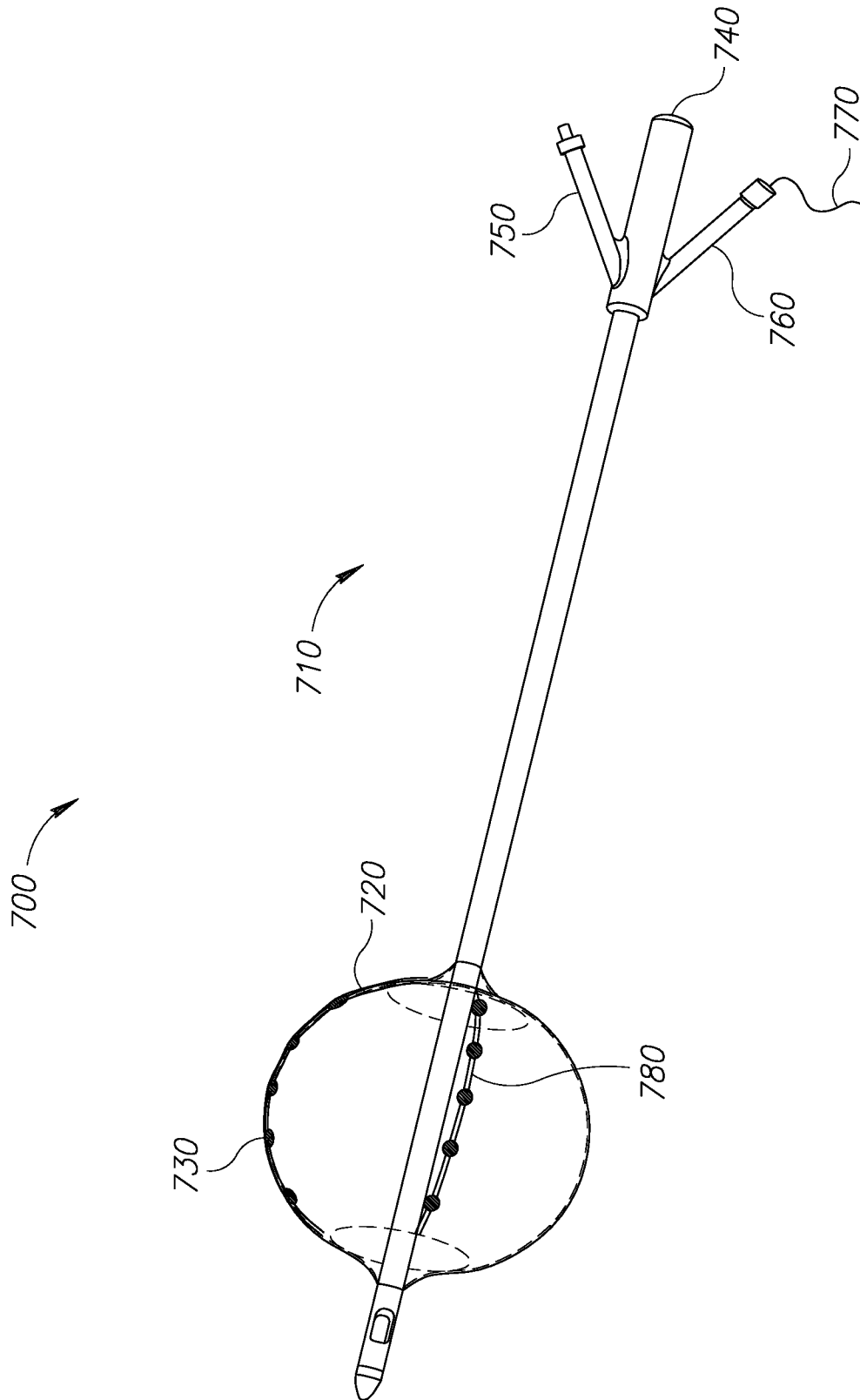


FIG. 7

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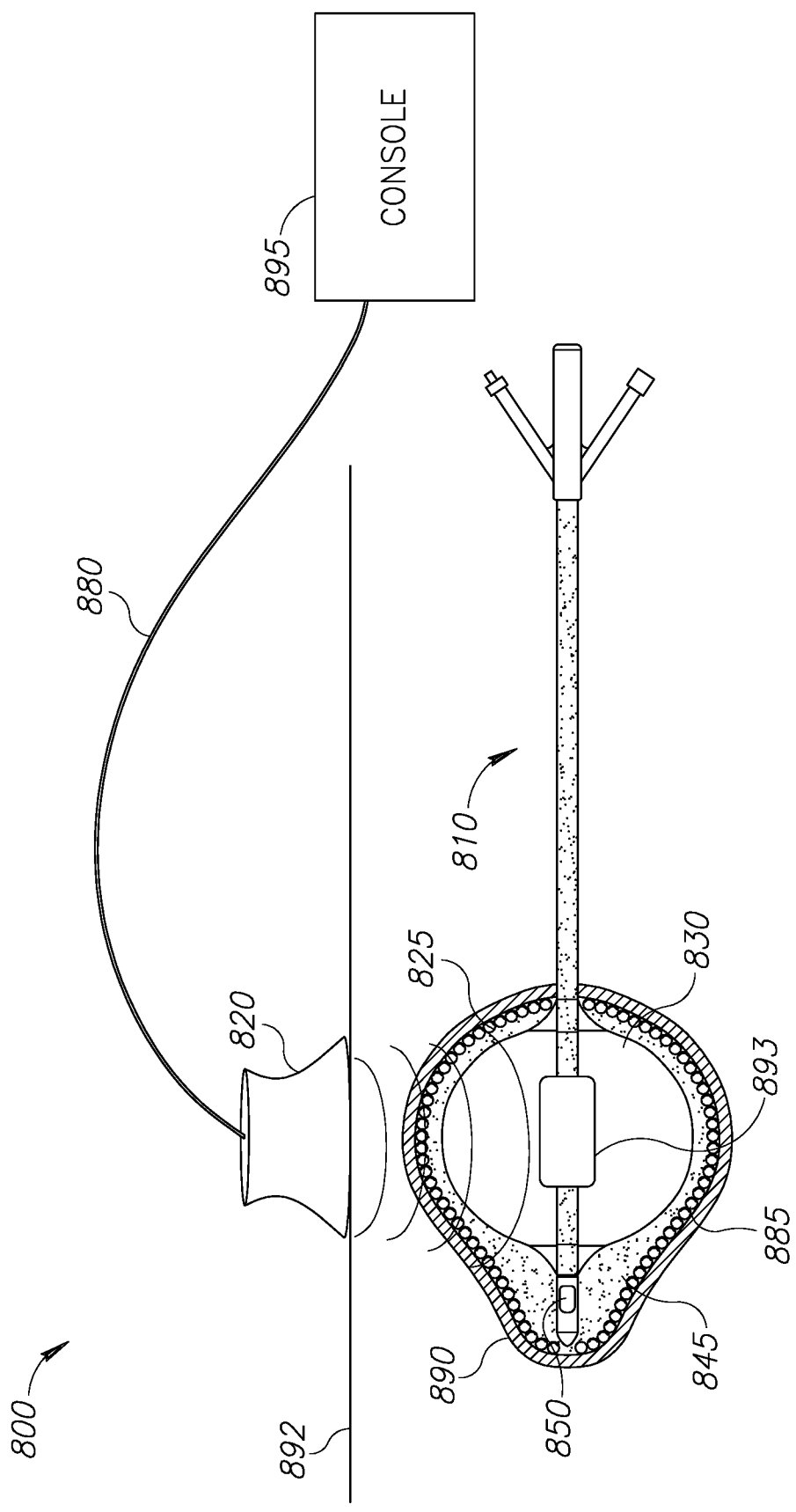


FIG.8

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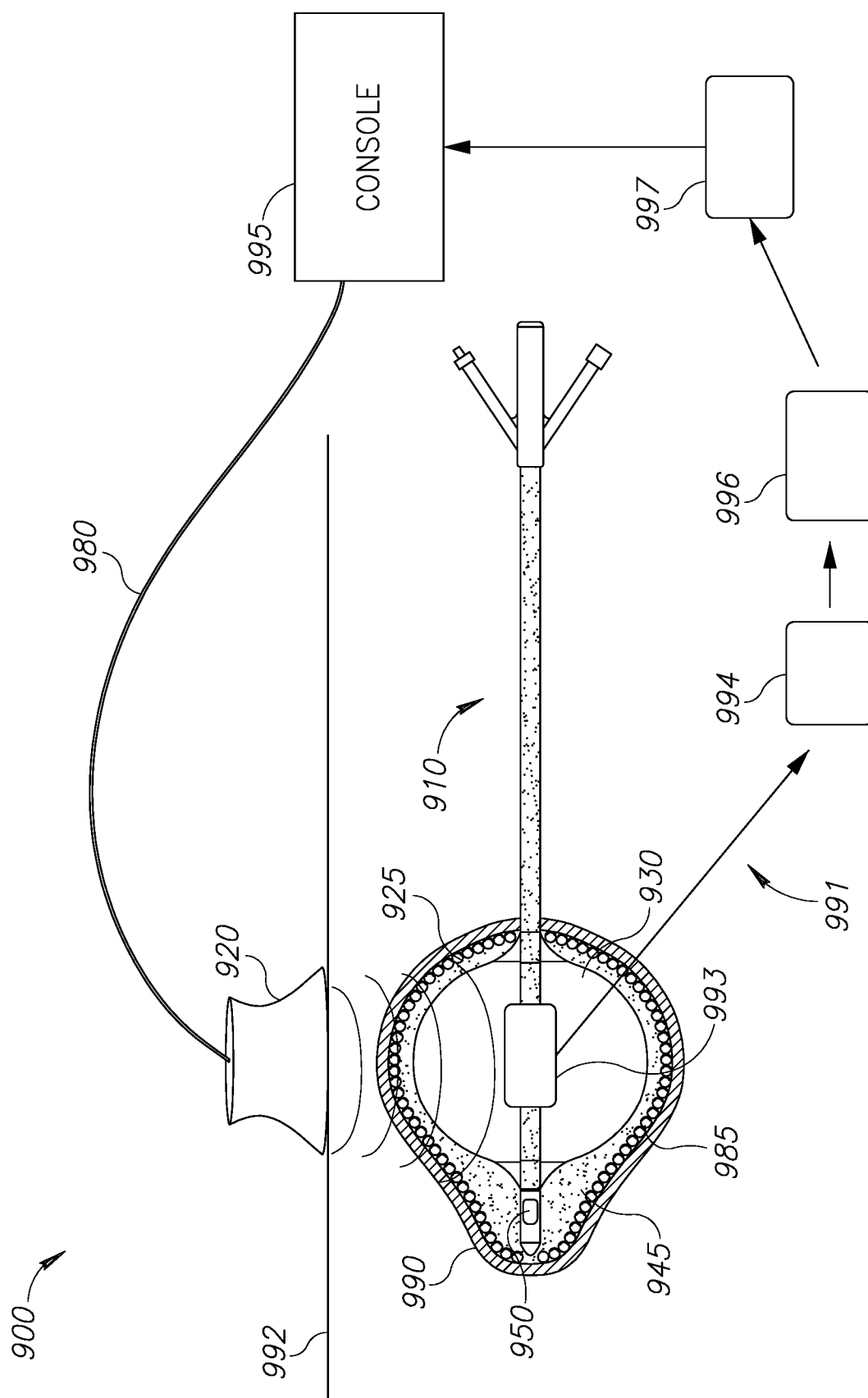


FIG. 9

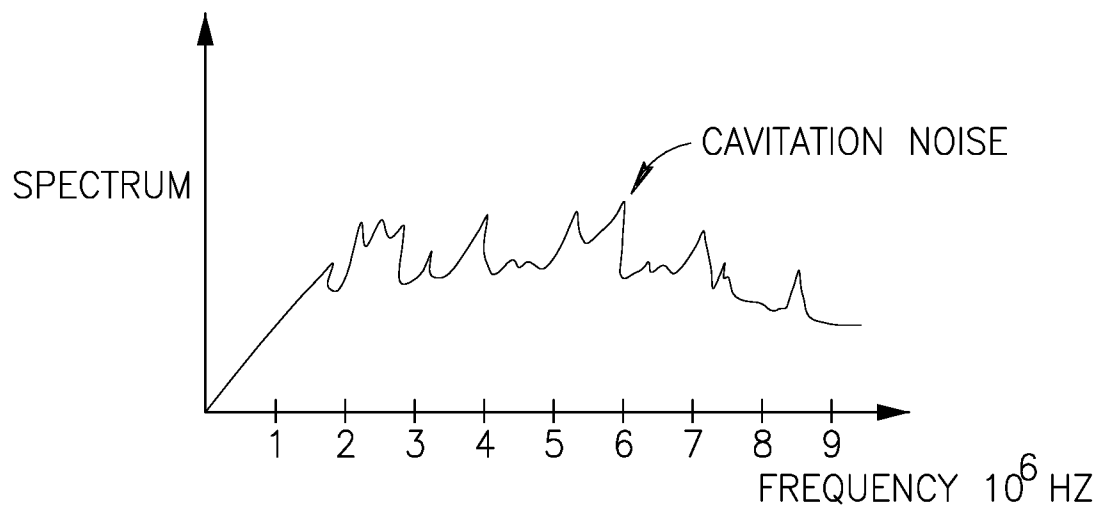


FIG.10A

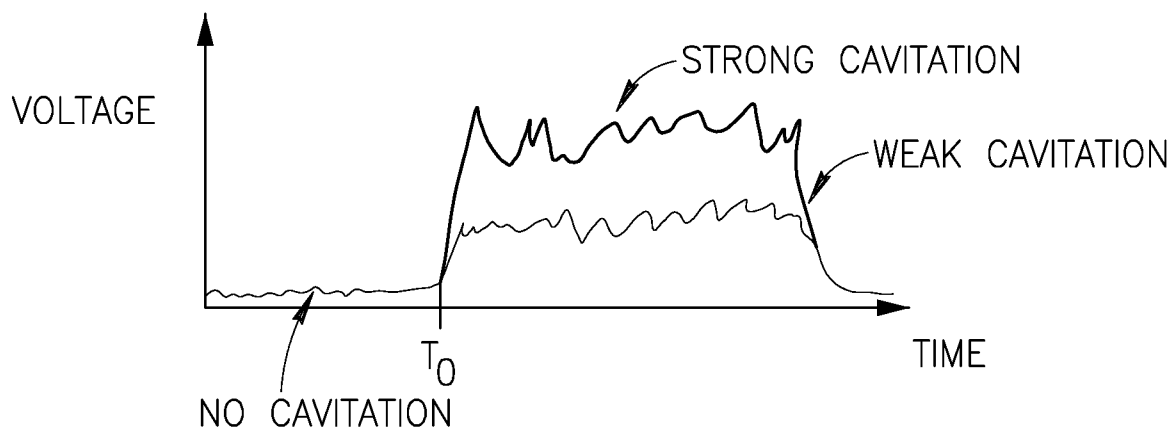


FIG.10B

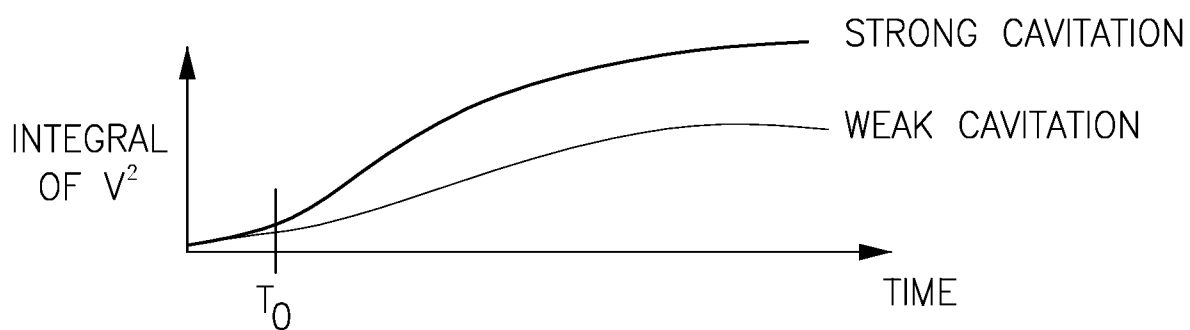


FIG.10C

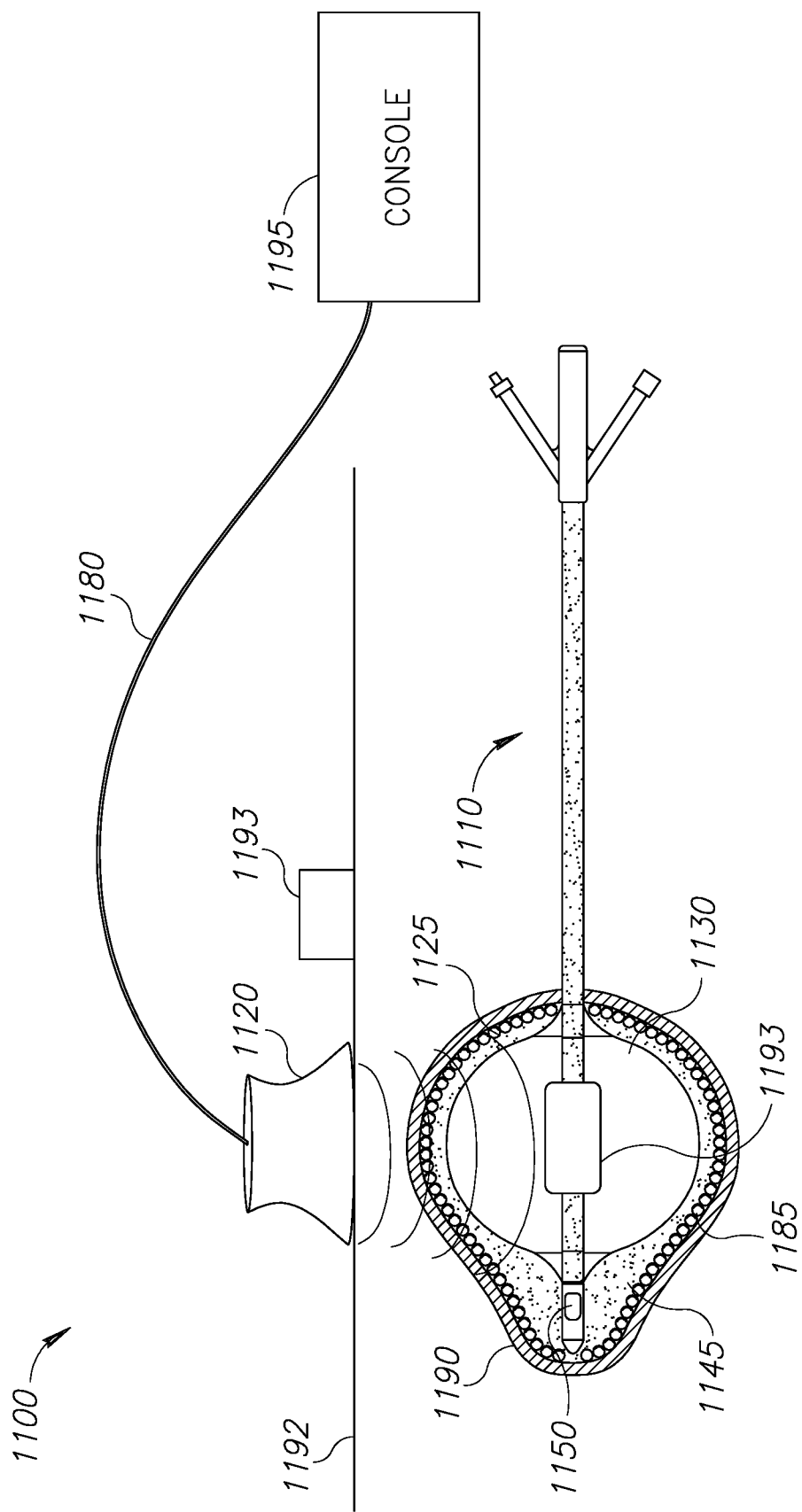


FIG. 11A

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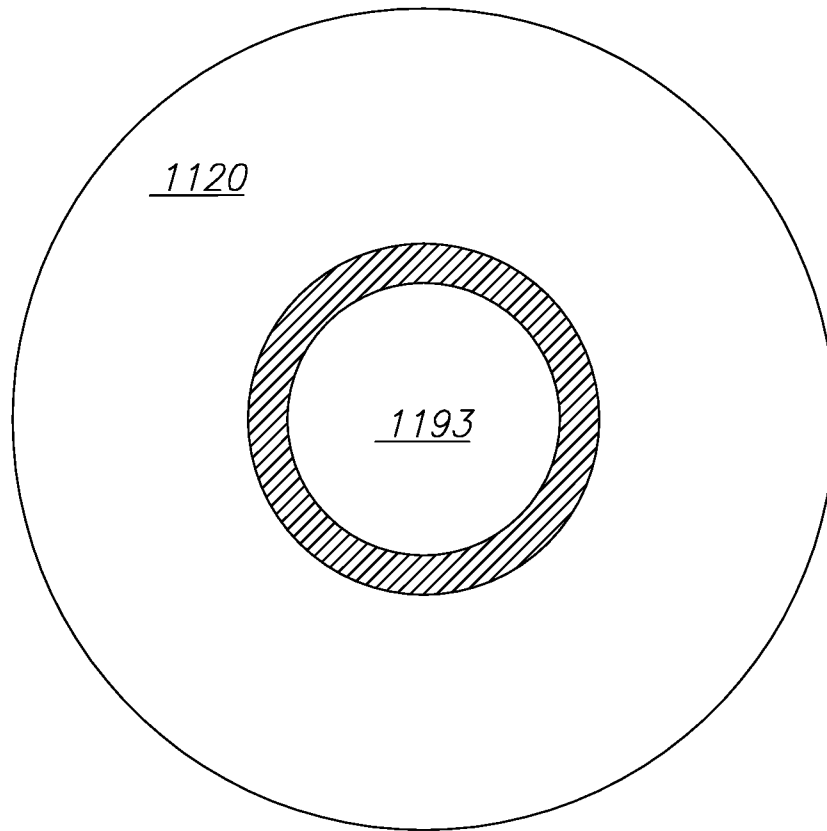


FIG.11B

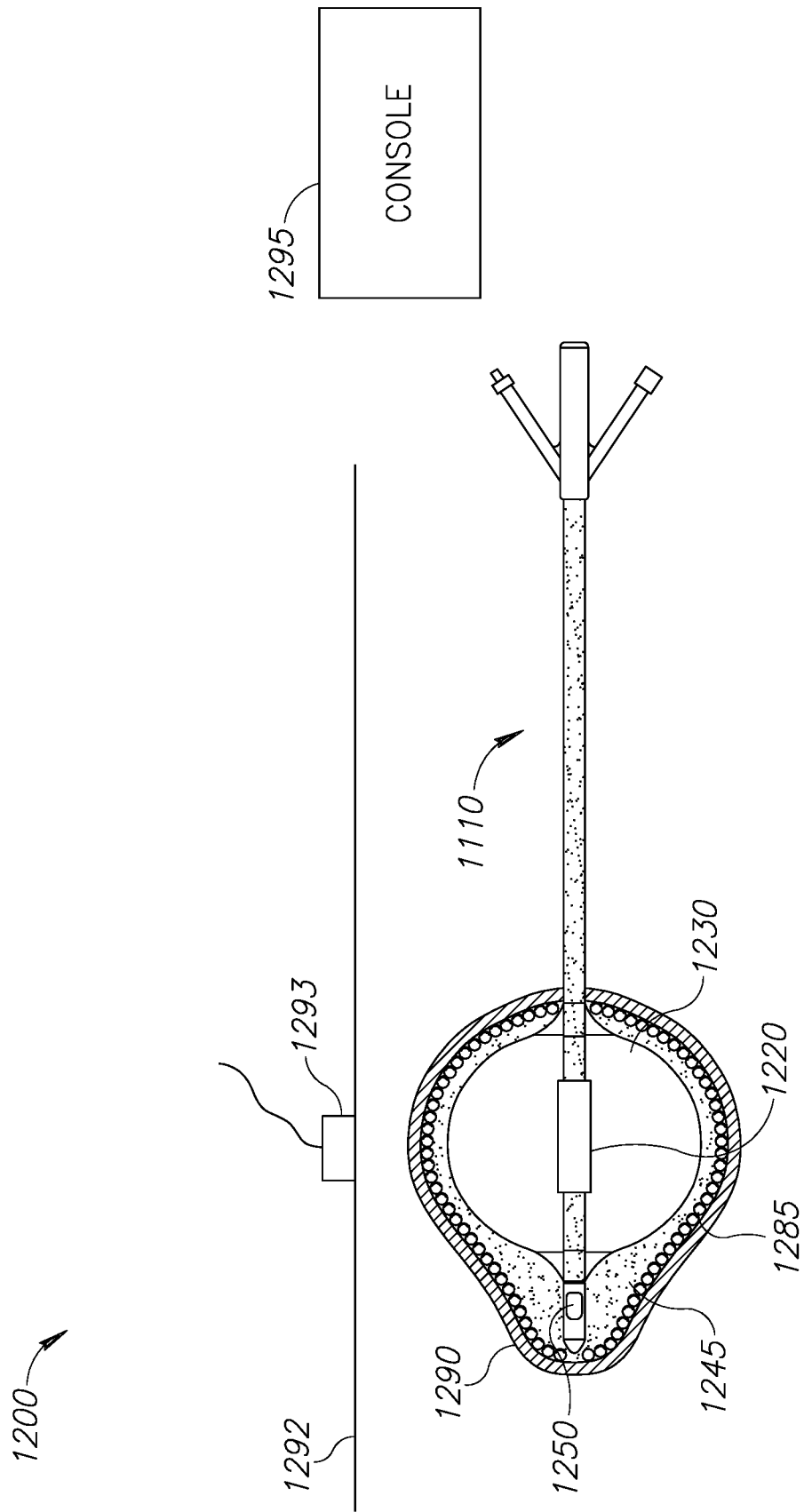


FIG.12

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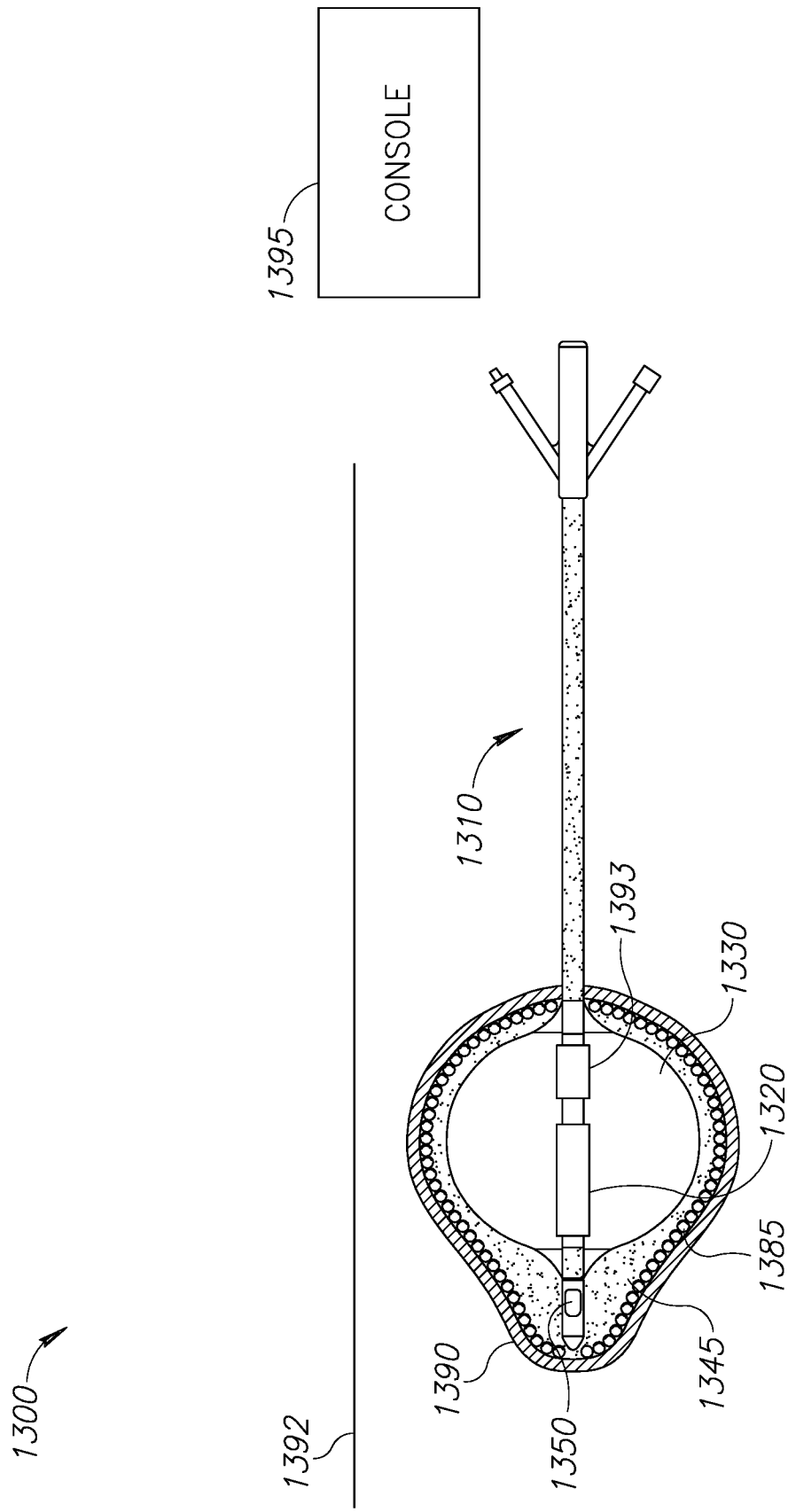


FIG.13

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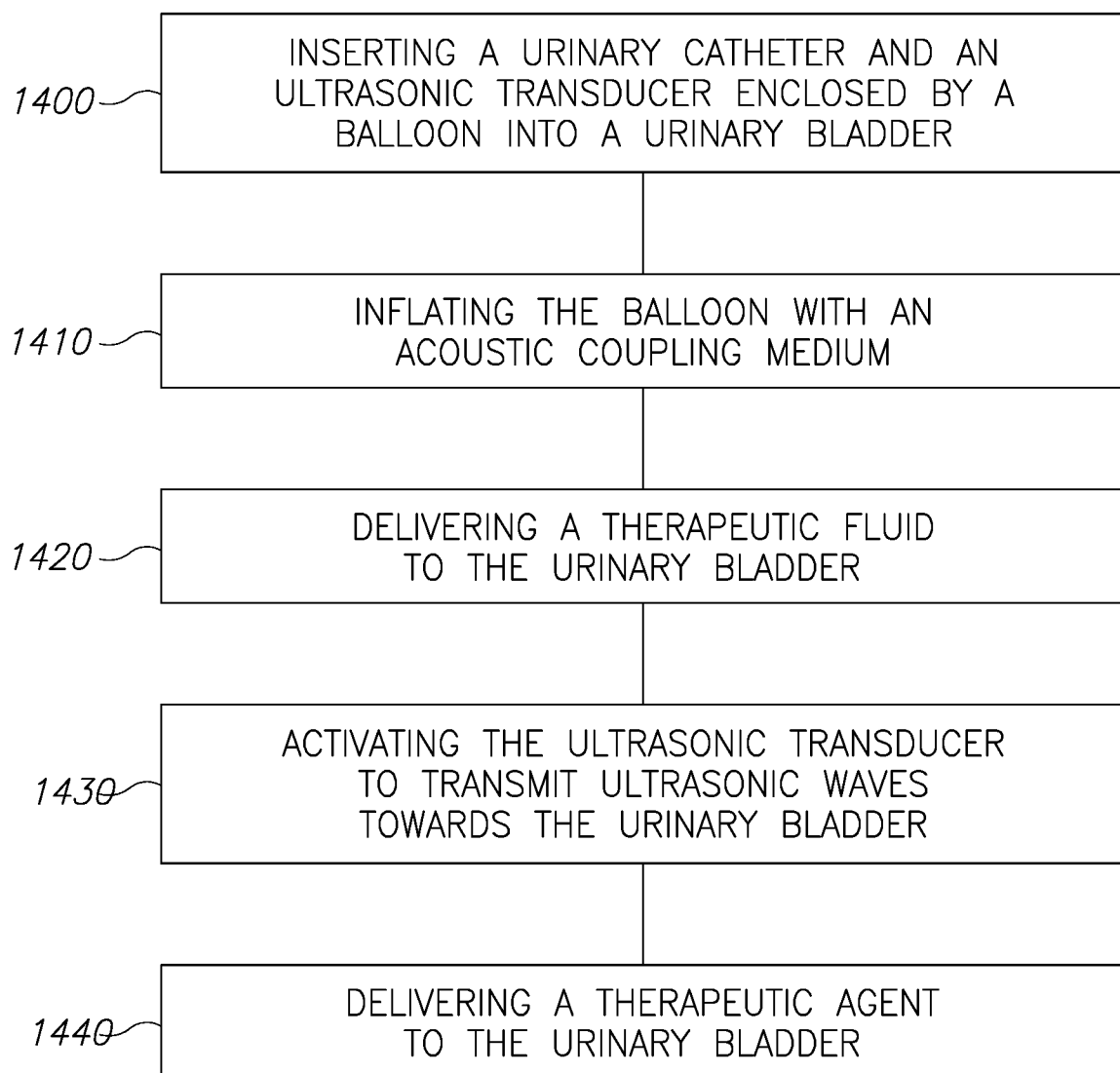


FIG.14

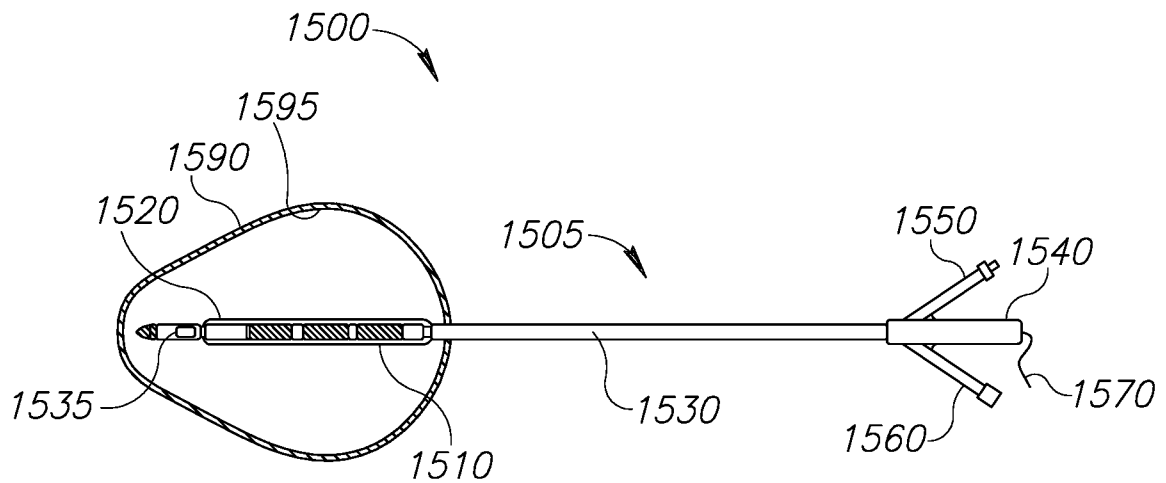


FIG.15A

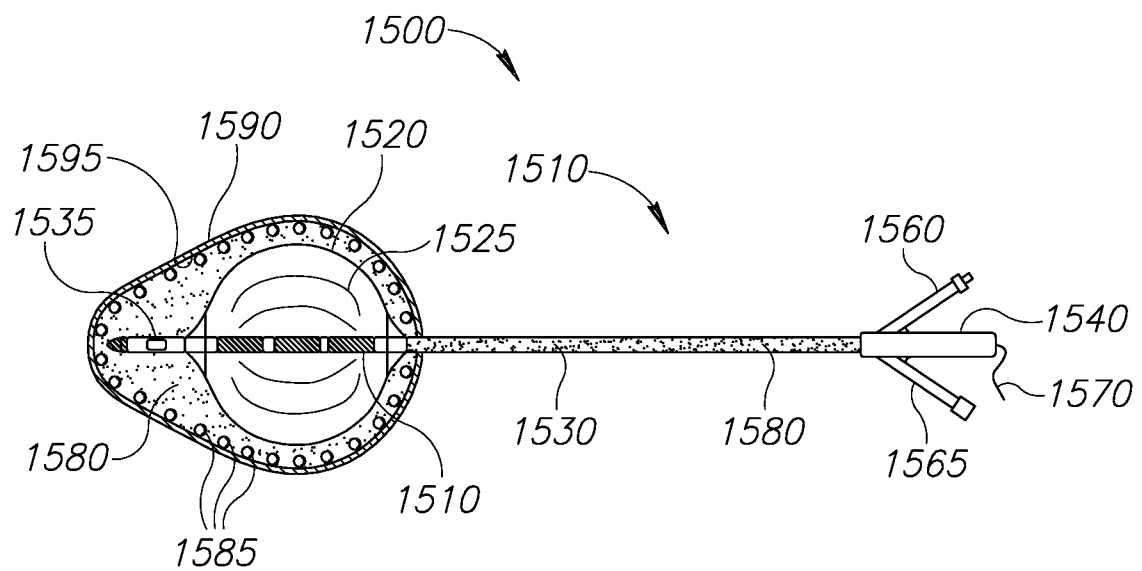


FIG.15B

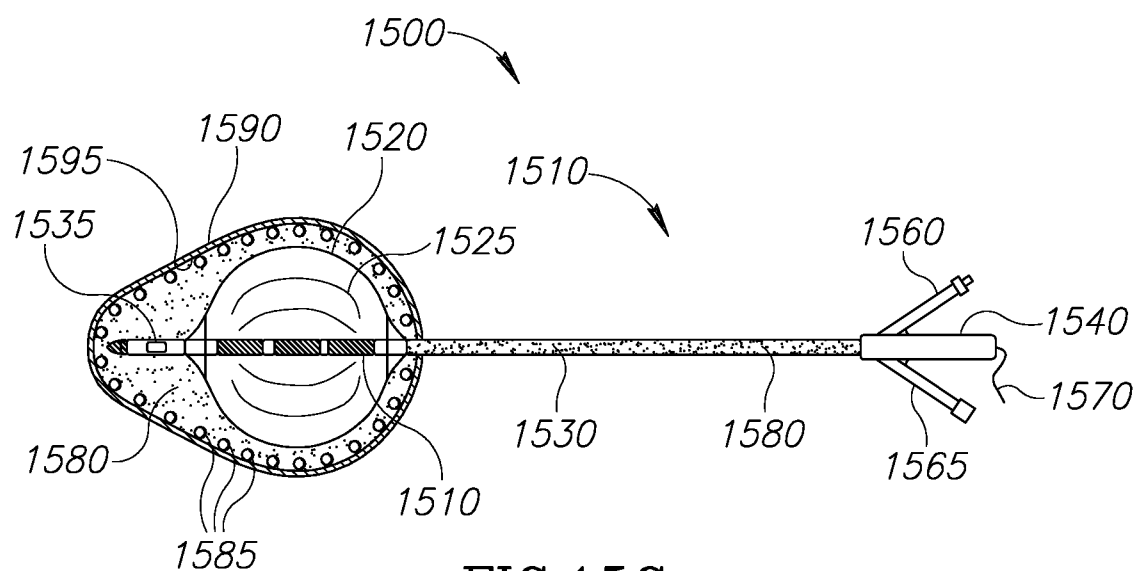


FIG.15C

INTERNATIONAL SEARCH REPORT

International application No.

PCT/IL2016/050326

A. CLASSIFICATION OF SUBJECT MATTER IPC (2016.01) A61M 37/00, A61M 25/10, A61N 7/00, A61K 41/00 According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC (2016.01) A61M, A61N Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) Databases consulted: Google Scholar, FamPat database, PatBase		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2003/0092667 A1 (TACHIBANA ET AL.) 15 May 2003 (2003/05/15) Abstract; paragraphs [0030], [0110]-[0112], [0119]-[0127], [0130], [0131], [0143], [0148]-[0150], [0187], [0268], [0281]; figures 3A-B, 5B, 9A-B, 16	1-9,12-20,25-44
Y		10,11,21-24
X	US 2003/0040712 A1 (RAY ET AL.) 27 Feb 2003 (2003/02/27) paragraphs [0021], [0022], [0030], [0035]; figure 3	1,4,16,25,32
Y	US 2013/0197555 A1 (RECOR MEDICAL, INC.) 01 Aug 2013 (2013/08/01) paragraphs [0031], [0114]-[0116]; figure 2b	10,21
Y	US 2011/0257523 A1 (HASTINGS ET AL.) 20 Oct 2011 (2011/10/20) paragraph [0137]; figure 8	11,22-24
☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.		
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Date of the actual completion of the international search 27 Jul 2016		Date of mailing of the international search report 28 Jul 2016
Name and mailing address of the ISA: Israel Patent Office Technology Park, Bldg.5, Malcha, Jerusalem, 9695101, Israel Facsimile No. 972-2-5651616		Authorized officer SEGAL Liviu Telephone No. 972-2-5651782

INTERNATIONAL SEARCH REPORT

International application No.

PCT/IL2016/050326

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5749845 A (IOTEK, INC.) 12 May 1998 (1998/05/12) the whole document	1-44
A	US 2012/0271167 A1 (UNIVERSITY OF CINCINNATI) 25 Oct 2012 (2012/10/25) the whole document	1-44
A	US 2012/0226230 A1 (GERRANS ET AL.) 06 Sep 2012 (2012/09/06) Abstract; paragraphs [0029], [0033]; figure 7D	25-44

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IL2016/050326

Patent document cited search report	Publication date	Patent family member(s)	Publication Date
US 2003/0092667 A1	15 May 2003	US 2003092667 A1	15 May 2003
		AU 5183096 A	23 Sep 1996
		AU 9500598 A	05 Apr 1999
		DE 69630285 D1	13 Nov 2003
		DE 69630285 T2	15 Jul 2004
		DE 69925122 D1	09 Jun 2005
		DE 69925122 T2	19 Jan 2006
		DE 69929523 D1	06 Apr 2006
		DE 69929523 T2	24 Aug 2006
		EP 0814719 A1	07 Jan 1998
		EP 0814719 B1	08 Oct 2003
		EP 1091699 A1	18 Apr 2001
		EP 1091699 B1	04 May 2005
		EP 1100385 A1	23 May 2001
		EP 1100385 B1	18 Jan 2006
		EP 1206771 A1	22 May 2002
		JP H11504534 A	27 Apr 1999
		JP 3955897 B2	08 Aug 2007
		JP H1192360 A	06 Apr 1999
		JP 4791616 B2	12 Oct 2011
		JP 2002519095 A	02 Jul 2002
		JP 4890674 B2	07 Mar 2012
		JP H08245420 A	24 Sep 1996
		JP 2002522108 A	23 Jul 2002
		JP 2003507105 A	25 Feb 2003
		US 6001069 A	14 Dec 1999
		US 6176842 B1	23 Jan 2001
		US 6210356 B1	03 Apr 2001
		US 6527759 B1	04 Mar 2003
		US 6582392 B1	24 Jun 2003
		US 6676626 B1	13 Jan 2004

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IL2016/050326

Patent document cited search report	Publication date	Patent family member(s)	Publication Date
		US 6723063 B1	20 Apr 2004
		US 2003153833 A1	14 Aug 2003
		US 7186246 B2	06 Mar 2007
		US 2003216681 A1	20 Nov 2003
		US 7413556 B2	19 Aug 2008
		US 2007149917 A1	28 Jun 2007
		US 7914509 B2	29 Mar 2011
		US 2005010112 A1	13 Jan 2005
		US 7976483 B2	12 Jul 2011
		US 2012095389 A1	19 Apr 2012
		US 8690818 B2	08 Apr 2014
		US 2012089082 A1	12 Apr 2012
		US 8764700 B2	01 Jul 2014
		US 2003157024 A1	21 Aug 2003
		US 2003167023 A1	04 Sep 2003
		US 2004015122 A1	22 Jan 2004
		US 2004059313 A1	25 Mar 2004
		US 2004229830 A1	18 Nov 2004
		US 2007112268 A1	17 May 2007
		US 2009105633 A1	23 Apr 2009
		US 2014155814 A1	05 Jun 2014
		US 2014343483 A1	20 Nov 2014
		WO 0000095 A1	06 Jan 2000
		WO 0007508 A1	17 Feb 2000
		WO 0113357 A1	22 Feb 2001
		WO 9627341 A1	12 Sep 1996
		WO 9848711 A1	05 Nov 1998
		WO 9913943 A1	25 Mar 1999
US 2003/0040712 A1	27 Feb 2003	US 2003040712 A1	27 Feb 2003
		US 7150738 B2	19 Dec 2006

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IL2016/050326

Patent document cited search report	Publication date	Patent family member(s)	Publication Date
		AU 2730401 A	16 Jul 2001
		US 6283947 B1	04 Sep 2001
		US 6494862 B1	17 Dec 2002
		US 2001007059 A1	05 Jul 2001
		US 6689099 B2	10 Feb 2004
		WO 0149357 A2	12 Jul 2001
		WO 0149357 A3	06 Dec 2001
US 2013/0197555 A1	01 Aug 2013	US 2013197555 A1	01 Aug 2013
		US 2004082859 A1	29 Apr 2004
		US 2013072928 A1	21 Mar 2013
		US 2013131668 A1	23 May 2013
US 2011/0257523 A1	20 Oct 2011	US 2011257523 A1	20 Oct 2011
		US 9192790 B2	24 Nov 2015
		EP 2558165 A2	20 Feb 2013
		JP 2013523412 A	17 Jun 2013
		WO 2011130531 A2	20 Oct 2011
		WO 2011130531 A3	15 Dec 2011
US 5749845 A	12 May 1998	US 5749845 A	12 May 1998
		EP 0805705 A1	12 Nov 1997
		JP H10512783 A	08 Dec 1998
		WO 9622806 A1	01 Aug 1996
US 2012/0271167 A1	25 Oct 2012	US 2012271167 A1	25 Oct 2012
US 2012/0226230 A1	06 Sep 2012	US 2012226230 A1	06 Sep 2012
		US 8348890 B2	08 Jan 2013
		CN 102600546 A	25 Jul 2012
		EP 2495007 A1	05 Sep 2012

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/IL2016/050326

Patent document cited search report	Publication date	Patent family member(s)	Publication Date
		US 2013165769 A1	27 Jun 2013
		US 9186485 B2	17 Nov 2015
		US 2015290438 A1	15 Oct 2015